10th Erciyes Medical Genetics Congress with International Participation

INVITED SPEAKER ABSTRACTS

IS1- Ailevi Akdeniz Ateşi Tanısı için Yenilikçi bir Optik Biyosensör Platformu

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Familial Mediterranean Fever (FMF) is a monogenic autoinflammatory disease, particularly prevalent among Mediterranean populations. It arises from mutations in the MEFV gene, which lead to abnormal regulation and overproduction of the pyrin protein—an intracellular sensor involved in innate immune responses. While genetic testing remains the gold standard for FMF diagnosis, it is often limited by high costs, restricted availability, and ambiguous interpretation, especially in heterozygous individuals. To address these limitations, we developed a novel plasmonic biosensing platform that enables direct quantification of pyrin protein levels in biological samples. The sensor integrates gold nanoparticle-functionalized surfaces with anti-pyrin antibodies, forming a selective and label-free detection interface. Coupled with an optofluidic system and visible light spectroscopy, the platform allows real-time monitoring of pyrin concentrations without the need for enzymatic or fluorescent labeling. Our device achieved a detection limit of 0.24 ng/mL and exhibited excellent stability, maintaining consistent signal performance for up to six months. In clinical validation tests, the biosensor successfully distinguished FMF patients from healthy controls with high sensitivity and specificity, demonstrating its capability for early and accurate diagnosis. The portability, rapid analysis time, and cost-effectiveness of the system further support its potential for integration into routine clinical workflows and point-of-care applications. This biosensing approach introduces a paradigm shift in FMF diagnostics, enabling more accessible and definitive testing, particularly in regions with limited access to genetic analysis. It also opens new avenues for protein-based screening of other autoinflammatory diseases.

Keywords: Plasmonics, Label-Free Biosensing, Optofluidics, FMF, Rare-Disease,

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IS2- Nadir Solid Tümör Kordomada Ferroptozis Mekanizması

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Kordoma, embriyonik notokord kalıntılarından köken alan nadir görülen bir kemik tümörüdür. Genellikle omurga hattı boyunca, özellikle kafatası tabanı (klivus) ve sakrum bölgelerinde lokalize olur. Histopatolojik olarak konvansiyonel, kondroid ve dediferansiye olmak üzere üç alt tipe ayrılır. Kordoma tedavisinde temel yaklaşımlar en blok rezeksiyon ve radyoterapi olmakla birlikte, günümüzde hastalık için onaylanmış etkili bir sistemik ilaç tedavisi bulunmamaktadır. Düzenlenmiş hücre ölümlerinin indüklenmesi, hedefe yönelik kanser tedavilerinde önemli bir strateji haline gelmiştir. Bu bağlamda, ferroptozis —demir bağımlı, lipid peroksidasyona dayalı programlanmış bir hücre ölümü türü— özellikle Erastin ve RSL3 gibi ajanlar aracılığıyla tetiklenebilmektedir. Bu çalışmada, kordoma hücrelerinde ferroptozisin etkileri araştırılmıştır.
Yapılan deneylerde, IC50 dozunda uygulanan Erastin sonrası kordoma hücrelerindeki SLC7A11 protein düzeyleri Western blot analizi ile değerlendirilmiştir. Hücre içi reaktif oksijen türleri (ROS) düzeyleri akış sitometrisi yöntemiyle analiz edilmiştir. Ayrıca, hücre proliferasyonunu ve tümöral potansiyeli değerlendirmek amacıyla koloni oluşumu ve tümör küre deneyleri gerçekleştirilmiştir. Bağışıklık kaçış mekanizmalarından biri olan PD-L1 ekspresyon düzeyleri de yine akış sitometrisi ile incelenmiştir.
Çalışmamızda, Erastin uygulanan kordoma hücrelerinde SLC7A11 protein düzeylerinde artış gözlenmiş, buna karşın hücre içi ROS seviyelerinde anlamlı bir değişiklik saptanmamıştır. Erastin tedavisi, hücre proliferasyonunu baskılamış, koloni oluşumunu engellemiş ve tümör küre oluşturma kapasitesini belirgin şekilde azaltmıştır. Ayrıca, Erastin uygulamasıyla birlikte PD-L1 ekspresyonunda artış tespit edilmiştir.
Bu bulgular, Erastin'in hücre ölümünü tetiklediğini ve hücre çoğalmasını engellediğini göstermektedir. PD-L1 düzeyindeki artış, ferroptotik yanıtın kordomada immünoterapi açısından potansiyel bir pencere oluşturabileceğine işaret etmektedir. Öte

yandan, SLC7A11 ekspresyonundaki artış, klasik ferroptozis mekanizmasının ötesinde, yeni tanımlanan düzenlenmiş hücre ölüm türlerinden biri olan disülfidoptozisin de bu süreçte rol oynayabileceğini düşündürmektedir. Bu nedenle, kordomada disülfidoptozisin araştırılması ileri çalışmalarda önemli bir odak noktası olabilir.

IS3- Diagnostic Power of Third-Generation Sequencing Technologies in Rare Genetic Disorders

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Rare diseases constitute a significant health burden both individually and globally. Over 80% of these disorders are of genetic origin, with the majority presenting in childhood. Despite advances in genetic testing, many patients remain undiagnosed for years, leading to a frustrating and often exhausting diagnostic odyssey for families and clinicians alike.

Short-read sequencing technologies, while effective in identifying many types of genetic variation, have notable limitations in detecting repetitive sequences, large structural variants, phasing, and deep intronic mutations. These constraints hinder the diagnostic yield in complex or unsolved genetic cases.

Third-generation sequencing technologies offer a transformative approach by enabling the continuous reading of long DNA molecules. Their advantages include real-time sequencing, PCR-free library preparation, simultaneous detection of epigenetic modifications, and the ability to resolve repetitive and structurally complex genomic regions. These capabilities make them especially powerful in addressing previously undiagnosable cases.

This presentation highlights the diagnostic contributions of long-read sequencing in rare disease cohorts, particularly in neurological and developmental disorders. Key applications discussed include structural variant analysis, detection of tandem repeat expansions, and variant phasing, where long-read sequencing technologies demonstrate clear technical superiority over traditional methods.

In conclusion, third-generation sequencing represents a critical advancement in the molecular diagnosis of rare diseases. Its integration into clinical workflows can significantly improve diagnostic rates, reduce time to diagnosis, and support the implementation of individualized medicine strategies.

IS4- Current Status of Gene Editing Therapies in Hematological Diseases

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Gene editing has revolutionized the treatment landscape for hematological disorders, offering unprecedented precision in correcting underlying genetic defects. This rapidly evolving field is moving from experimental stages to approved clinical applications, transforming the lives of patients with previously intractable conditions. Gene Editing Technologies include TALENs (Transcription Activator-Like Effector Nucleases) and ZFNs (Zinc Finger Nucleases), which also enable targeted DNA modifications. More recent innovations like base editing and prime editing offer even greater precision, allowing for single-nucleotide changes or small insertions/deletions without inducing double-strand breaks, potentially reducing off-target effects.The cornerstone of these advancements lies in powerful gene editing tools. CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein 9) is the most prominent, known for its efficiency and relative ease of use in making precise cuts in DNA.

Delivery Methods and Challenges; Effective delivery of gene editing components to target cells remains a critical challenge. Common strategies include: Ex vivo editing:Hematopoietic stem cells are harvested from the patient, edited in the lab, and then reinfused. This method is highly controlled but invasive. In vivo editing: Gene editing components are delivered directly into the patient's body, often using viral vectors(e.g., adeno-associated viruses - AAV) or lipid nanoparticles (LNPs). This approach is less invasive but faces challenges with targeting specificity and potential immunogenicity.

Major challenges that are actively being addressed include:

Off-target effects:Unintended edits at non-target sites can lead to safety concerns.Delivery efficiency and specificity:Ensuring the editing machinery reaches the correct cells in sufficient quantities. Immunogenicity: The body's immune response to gene editing components or delivery vectors. Long-term efficacy and safety: Understanding the durability of the edits and potential long-term complications. Cost and accessibility: Gene editing therapies are currently very expensive, limiting their widespread availability.

The applications in hematological diseases are Gene editing therapies that are being explored and developed for a wide range of hematological disorders: **Sickle Cell Disease (SCD) and Beta-Thalassemia**:These are among the most advanced areas. Gene editing aims to reactivate fetal hemoglobin (HbF) production (e.g., by targeting the BCL11A gene) or to directly correct the disease-causing mutations in the beta-globin gene. Several clinical trials have shown promising results, with some patients achieving transfusion independence and significant symptom improvement.**Severe Combined Immunodeficiency (SCID):** Gene editing can correct the genetic defects in hematopoietic stem cells, restoring a functional immune system in patients with various forms of SCID, such as ADA-SCID. **Hemophilia:**While gene therapy (gene addition) has seen success, gene editing approaches are being explored to achieve more durable and potentially curative solutions by correcting the faulty coagulation factor genes directly in hepatocytes. **Fanconi Anemia (FA):**This rare genetic disorder leads to bone marrow failure. Gene editing holds promise for correcting the defective genes in hematopoietic stem cells to prevent progressive

bone marrow failure and reduce cancer risk. **Acute Myeloid Leukemia (AML) and Lymphoma:** Beyond correcting genetic defects, gene editing is also being used to enhance CAR T-cell therapy. By editing the T-cells themselves (e.g., to remove PD-1 or other inhibitory receptors, or to insert specific chimeric antigen receptors), their anti-cancer efficacy and persistence can be significantly improved. Future Therapies; The field of gene editing for hematological diseases is rapidly advancing. With ongoing research, improved delivery systems, and enhanced specificity of editing tools, it is anticipated that more gene-edited therapies will gain regulatory approval. The focus is shifting towards making these curative treatments safer, more accessible, and applicable to a broader range of genetic blood disorders, ultimately offering new hope for patients worldwide.

IS5- Unveiling the role of a deSUMOylating isopeptidase in a new ALS like syndrome

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Background: Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative syndrome primarily affecting the motor neuron system and is undoubtedly associated with genetic predisposition. Despite the identification of over 40 ALS-related genes, many patients remain without a genetic diagnosis, highlighting the complexity of its underlying pathogenesis. Identifying novel genetic variants is essential for improving diagnostics and developing targeted treatments.

Materials and Methods: Whole Exome Sequencing (WES) was employed to investigate genetically undiagnosed ALS-like cases, leading to the identification of two distinct recessive mutations in *DESI1*, a deSUMOylase enzyme, in two unrelated families. Functional studies including cloning, immunoblotting, immunofluorescence staining, and co-immunoprecipitation, were conducted using *DESI1* mutant patient-derived fibroblast and CRISPRi knockdown in SH-SY5Y neuroblastoma cells to investigate molecular pathomechanisms.

Results: *DESI1* variants cause protein truncation and instability, resulting in degradation and likely loss-of-function. Remarkably, DESI1 interacts with ALS-associated proteostasis regulators, including UBQLN1, 2, and 4, highlighting its potential role in ALS pathogenesis. The UBQLN4-DESI1 complex mediates the nuclear export of polyubiquitinated proteins to the cytosol. Notably, *DESI1* mutant cells exhibited defective nuclear export, leading to the aberrant accumulation of polyubiquitinated proteins, a well-known hallmark of ALS.

Conclusion: Our findings establish *DESI1* as a novel genetic cause of ALS-like syndrome and suggest that physicians should consider this gene as a potential candidate in genetically undiagnosed cases. DESI1, sharing the same pathogenic pathways with known ALS-associated proteins, is a promising target for developing neuroprotective treatments strategies in a broader range of ALS patients.

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References

1. Mead RJ, Shan N, Reiser HJ, Marshall F, Shaw PJ. Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery. 2023 Mar;22(3):185-212.
2. Wang H, Guan L, Deng M. Recent progress of the genetics of amyotrophic lateral sclerosis and challenges of gene therapy. Frontiers in neuroscience. 2023 May 12;17:1170996.
3. Hirayama S, Sugihara M, Morito D, Iemura SI, Natsume T, Murata S, Nagata K. Nuclear export of ubiquitinated proteins via the UBIN-POST system. Proceedings of the National Academy of Sciences. 2018 May 1;115(18):E4199-208.
4. González-Pérez P, Lu Y, Chian RJ, Sapp PC, Tanzi RE, Bertram L, McKenna-Yasek D, Gao FB, Brown Jr RH. Association of UBQLN1 mutation with Brown–Vialetto–Van Laere syndrome but not typical ALS. Neurobiology of disease. 2012 Dec 1;48(3):391-8.
5. Deng HX, Chen W, Hong ST, Boycott KM, Gorrie GH, Siddique N, Yang Y, Fecto F, Shi Y, Zhai H, Jiang H. Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS/dementia. Nature. 2011 Sep 8;477(7363):211-5.
6. Edens BM, Yan J, Miller N, Deng HX, Siddique T, Ma YC. A novel ALS-associated variant in UBQLN4 regulates motor axon morphogenesis. Elife. 2017 May 2;6:e25453.

IS6- Genetic etiopathogenesis of Charcot-Marie-Tooth disease and emerging novel treatment options

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Charcot-Marie-Tooth (CMT) disease is characterized by progressive motor and sensory nerve dysfunction leading to distal muscle weakness and atrophy and is one of the most common hereditary neuromuscular disorders with a prevalence of 1:2500. The most common form is CMT1a and it is related to *PMP22* duplications leading to overexpression. The other common associated genes are *GJB1*, *MFN2*, *MPZ*, *SH3TC2* and *SORD*. There are no curative treatments for CMTs yet. However, there are promising results by in vitro and in vivo preclinical studies including RNA, antisense oligonucleotides or CRISPR/Cas9 mediated downregulation of *PMP22* expression in mice models as well as lentiviral or AAV-mediated gene therapies for the other common CMT forms. There are also some significant pathways targeted for the treatments of specific CMT types such as *SARM1* pathway for axonal CMTs and unfolded protein response (UPR) pathway for CMT1B. The most probable novel treatments expected in the near future are aldose reductase inhibitors for *SORD*-related CMT forms due to their promising results in the ongoing phase III clinical study. The other expected novel treatments for which phase I / II clinical studies are going on are sephin-1 targeting UPR pathway, and AAV-mediated neurotrophin-3 gene therapy which is crucial for Schwann cell autocrine survival and regeneration.
Key words: Charcot-Marie-Tooth disease; inherited neuropathy; *PMP22*; gene therapy; aldose reductase inhibitors

ORAL PRESENTATION ABSTRACTS

OP1- Whole genome characterization of probiotic *Latilactobacillus sakei* isolated from traditional Turkish pastrami: A functional genomics perspective on health-promoting bacteria

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Abstract

Probiotics are defined as live microorganisms that confer a documented health benefit on the host by interacting with gut microbiota and other host biological systems. Among them, lactic acid bacteria (LAB) play a significant role in promoting gastrointestinal and immune health and providing protection against pathogens. Fermented foods serve as natural reservoirs for LAB strains with potential probiotic properties. In this study, traditional Turkish pastrami, a fermented meat product typically consumed without heat treatment, was investigated as a source of beneficial LAB. A total of 49 LAB isolates were obtained from ready-to-eat pastrami samples collected from multiple production facilities in Kayseri. Initial screening was performed based on phenotypic and biochemical characteristics, followed by species-level identification using MALDI-TOF MS and 16S rRNA gene sequencing. Phylogenetic clustering was used to analyze the relationships among the isolates. Functional probiotic properties of the isolates were evaluated through *in vitro* experiments assessing resistance to simulated gastric and intestinal fluids, salt and acid tolerance, and adhesion capability to human colorectal adenocarcinoma cell lines (Caco-2). The whole genome sequencing was conducted on the most promising isolate, revealing genes associated with adhesion, acid and stress tolerance, antibiotic resistance, and antimicrobial peptide production. The findings demonstrated that certain *Latilactobacillus sakei* strains from pastrami possess significant probiotic potential at the molecular level. This study highlights the health-promoting potential of traditionally fermented meat products and supports their classification as functional foods. Integrating genomic and functional data aims to contribute to public health through evidence-based food choices.

Keywords: Healthy Nutrition, functional foods, next generation sequencing, adhesion assay.

OP2- A *de novo* pathogenic FOXG1 frameshift mutation associated with autosomal dominant congenital Rett Syndrome

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Abstract

Congenital Rett syndrome (OMIM #613454), an autosomal dominant ultra-rare neurodevelopment disorder that is characterised by the clinical presentation of early developmental delay, severe verbal impairment, and abnormal movement which shown in earlier onset in the first months of life. The case demonstrates the value of ruling out *FOXG1* mutations in a male neonate with marked neurodevelopment abnormality and epileptiform EEG findings shortly after birth, prompting referral for genetic investigation. The *FOXG1* gene encodes a transcriptional repressor which is essential for the early brain development, including telencephalon formation and maturation, and plays an essential role in neuronal proliferation, differentiation, and regional cerebral hemispheres patterning. The presented patient exhibited significant neurodevelopment delay, abnormal breathing patterns, atypical motor movements, and abnormal electroencephalographic findings, prompting referral for genetic evaluation. Therefore, Trio-WES analysis using third generation Oxford Nanopore sequencing technology has been done to patient and both parents which revealed a heterozygous c.459_460delGG (p.Glu154fs) frameshift variant in *FOXG1,* only in patient. This variant has been identified as pathogenic in ClinVar and further confirmed by in-silico predictors such as Varsome and Franklin, with expected functional consequences including premature truncation of the *FOXG1* protein with the congenital form of Rett syndrome. Additionally, parental analysis established that the mutation was *de novo*, and there was no family history of such characteristics. Despite immediate medical attention, the patient died within 24 hours of life. This case underscores the diagnostic value of NGS in detecting *de novo* pathogenic variants and highlights the importance of considering *FOXG1*

mutations in neonates with unexplained severe neurologica symptoms. In conclusion, the detection of such mutations ma explain cases of early postnatal sudden death; therefore, long read whole-exome sequencing and comprehensive family-base genetic analysis are recommended in similar presentations.
Keywords: FOXG1, Rett syndrome, ultra-rare genetic disease, neurodevelopment disorder

OP3- Tool combination via machine learning significantly improves CNV detection success in WGS

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Introduction: Despite the development of numerous tools to detect copy number variations (CNVs) utilizing next-generation sequencing (NGS) data, no single tool performs consistently well across all CNV types and datasets. To improve accuracy, studies suggest using multiple tools. However, how to combine different CNV detection tool outputs still remains a challenge, and interpreting combined results is yet to be explored.
Materials&Methods: 11 CNV detection tools (Breakdancer, CNVpytor, GATK gCNV, Canvas, Control-FREEC, cn.MOPS, CNVkit, Delly, Gridss, Manta, Lumpy) were selected based on literature and internal evaluation. The well-characterized NA12878 whole genome sequencing (WGS) dataset and its validated gold-standard CNV set were used for benchmarking and machine learning. Tool outputs were initially merged using the SURVIVOR tool. Later, we applied a custom genome-wide binning strategy to integrate results and used machine learning models (Random Forest, Logistic Regression, XGBoost) with 5-fold cross-validation for CNV detection. The performance of each method was evaluated using precision, recall, and F1-score against the gold standard.
Results: Among individual tools, Delly achieved the highest F1-score (0.35). All possible tool combinations with SURVIVOR produced F1-scores reaching up to 0.45. Our integration approach using Random Forest significantly improved performance, yielding F1-scores of 0.91 for deletions and 0.71 for duplications.
Discussion&Conclusion: This study shows that machine learning-based integration of CNV tools can greatly improve CNV detection success, reaching levels comparable to microarray platforms. Even low-performing tools add valuable data when intelligently combined. These findings highlight th promise of AI-supported CNV detection from NGS data.
Keywords: CNV, machine learning, random forest, NGS

OP4- Computational Analysis of Histone Lactylation Complex Genes and their Role in the Pathogenesis of AML

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Introduction: AML is an aggressive hematologic malignancy characterized by impaired differentiation and uncontrolled proliferation of immature hematopoietic precursors. Recent findings highlight the growing significance of epigenetic modifications, particularly histone lactylation, in cancer biology. The aim of study is to comprehensively identify mutations and expression profiles in the genes forming the lactylation complex using bioinformatics tools, with a focus on understanding the underlying mechanisms.
Material and Methods: Genomic sequences and expression profiles of AML cohort (n:872) were acquired from using tools and analyzed. PolyPhen-2, SIFT, Mutation Assessor, and AlphaMissense tools were utilized to forecast the pathogenic effects of mutations determined in target genes encoding subunits of the Lactylation modulation complex. Furthermore, m-RNA expression and survival profiles were also invastigated.
Results: 7 mutations were detected in 8 genes. 3 mutations were classified as pathogenic. A deletion leading to a homozygous loss of allele was discovered in *ALKBH5*. Mutations with function-altering effects were identified in the codes encoding the domains of the genes. The frameshift mutations p.S250Kfs*9 and p.T343Rfs*26 discovered in *WTAP* have the potential to cause the formation of transcripts with impaired function by altering the reading frame. The pathogenic p.C472Y mutation was detected in the C-terminal region of *FTO* and the pathogenic p.R693H mutation in the RRM region of the *RBM15* gene. A pathogenic p.Q28R was detected in the RNA methylase region of *METTL5* and a p.Y128H mutation was detected in the LDH1 domain of the *LDHB*. The results of our m-RNA expression profiling showed that the expression levels of *LDHA* and *LDHB* were down-regulated in AML samples and up-regulated in *FTO* compared to healthy subjects. ($p<0.01$). The effect of gene expression on survival was found to be significant with decreased *ALKH5*. ($p=0.017$).
Discussion: Targeting lactate-driven histone modifications or/and epitranscriptomic pathways in hematological malignancies such as acute myeloid leukemia may enhance the effectiveness of immunotherapies.
KeyWords: Acute myeloid leukemia; Epigenetics; Lactylation; Mutation; Expression

OP5- NIPT screening outcomes in Northern Cyprus

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Objectives:

This study aims to evaluate the clinical utility of Non-Invasive Prenatal Testing (NIPT) in detecting chromosomal abnormalities among pregnant women and to describe the demographic and biological parameters associated with the test results.

Materials and Methods:

A retrospective analysis was conducted on 282 pregnant women who underwent NIPT in Cyprus. Maternal age, gestational week at testing, fetal fraction levels, as well as presence/absence of Y chromosome were recorded. The NIPT assessed risk levels for common trisomies, including Trisomy 21, 18, and 13. Descriptive statistics and inferential analyses were performed using Jamovi software.

Results:

The average maternal age was 35.38 years (SD ±7.81), and the mean gestational age at testing was 11.86 weeks (SD ±2.84). The mean fetal fraction was 18.7% (SD ±8.18), ranging from 3.0% to 92.0%. Of the 282 cases analyzed, only 2 were reported as "very high risk" for Trisomy 21, while 280 (99.29%) were classified as "very low risk" for all screened trisomies. No high-risk cases were identified for Trisomy 18 or 13.

Sex chromosome analysis indicated that 141 samples (51.1%) showed the presence of a Y chromosome, while the remaining 48.9% did not. A one-way Welch's ANOVA was performed to evaluate the relationship between fetal fraction and the presence of the Y chromosome. The results showed no statistically significant difference in fetal fraction between groups ($F(1, 273) = 0.215$, $p = 0.643$). Group means were 0.212 (SD ±0.867) for the presence and 0.166 (SD ±0.785) for the absence of the Y chromosome. Additionally, a chi-square test assessing the association between fetal fraction and the presence of the Y chromosome showed no significant relationship ($p = 0.546$).

Conclusion:

NIPT proved to be a highly effective and non-invasive screening method for early detection of chromosomal abnormalities, with the majority of cases presenting as very low risk. Neither the presence of a Y chromosome nor the fetal fraction showed a significant statistical relationship, further supporting the robustness of NIPT across fetal sex. These findings support the routine use of NIPT in prenatal care, particularly for women of advanced maternal age, as a means to reduce reliance on invasive diagnostic procedures.

Keywords: NIPT, Prenatal Screening, Trisomy 21, Fetal DNA, Chromosomal Abnormalities, Fetal Fraction

OP6- Clinical and molecular features of a COXPD12 case with compound heterozygous variants in the EARS2 gene

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Introduction

EARS2 encodes mitochondrial glutamyl-tRNA synthetase, which is essential for mitochondrial protein synthesis. Biallelic pathogenic variants cause combined oxidative phosphorylation deficiency 12 (COXPD12, OMIM #614924), a rare autosomal recessive disorder characterised by infantile-onset hypotonic encephalopathy, psychomotor regression, basal ganglia involvement and lactic acidosis. In this report, we present a COXPD12 case carrying compound heterozygous variants in the *EARS2* gene with seizures, motor developmental delay and characteristic MRI findings.

Materials and Methods

A male patient presented at the age of 10 years with vomiting, diarrhoea and seizures. Neurological examination revealed microcephaly, brachycephaly, dysmetria, involuntary movements and motor delay. Brain MRI showed bilateral basal ganglia involvement and lactate peaks. Metabolic studies were unremarkable. Next-generation sequencing was performed using a targeted mitochondrial gene panel. Variant interpretation followed ACMG guidelines and in silico pathogenicity tools.

Results

Compound heterozygous variants in *EARS2* were identified: p.(Ala272Thr) [rs749912939], previously reported as likely pathogenic, and p.(Gly301Ala), classified as a variant of uncertain significance (VUS). The clinical phenotype was consistent with COXPD12, supporting the pathogenic relevance of the detected variants. The patient was treated with levetiracetam with good seizure control, although motor improvement remained limited.

Conclusions

This case highlights the importance of considering *EARS2* mutations in infants with early-onset seizures, microcephaly and basal ganglia involvement. Molecular diagnosis is crucial for the identification of COXPD12 and for appropriate genetic counselling. Phenotype-genotype correlation may help to clarify the clinical significance of rare or uncertain variants.

OP7- Prenatal diagnosis of Prader-Willi syndrome due to maternal mixed iso/hetero uniparental disomy

Eyyüp Üçtepe - Acıbadem Labgen Genetik Hastalıklar Tanı Merkezi

Prader-Willi Syndrome (PWS) is a complex genetic disorder marked by neonatal hypotonia, poor feeding in infancy, later development of hyperphagia, obesity, cognitive deficits, behavioral abnormalities, and endocrine dysfunction, including hypogonadism and short stature. While the postnatal phenotype is well established, prenatal diagnosis remains challenging due to the absence of a consistent fetal presentation.

This case report presents a fetus diagnosed prenatally with PWS caused by maternal uniparental disomy of chromosome 15 (UPD15). Chromosomal microarray analysis (CMA) on amniotic fluid revealed a 35 Mb region of loss of heterozygosity (LOH) at 15q22.2q26.2. Combined with prior non-invasive prenatal testing (NIPT) results showing elevated risk for Trisomy 15, the findings suggested a trisomy rescue event. Further molecular karyotyping of both parents confirmed the maternal origin of both chromosome 15 copies in the fetus. Segmental analysis identified mixed heterodisomy and isodisomy, with the PWS-critical region (15q11.2–q13) located within the heterodisomic segment, confirming the genetic basis of PWS in this case. The family received genetic counseling regarding the expected clinical outcome and chose to terminate the pregnancy.

This case underscores the utility of integrated genomic technologies—NIPT, CMA, and parental studies—in identifying UPD-related syndromes. It also highlights the relevance of recognizing UPD15 as a pathogenic mechanism of PWS, enabling timely diagnosis and family-centered decision-making even in the absence of prenatal ultrasound findings.

Keywords: Prader-Willi Syndrome; Uniparental disomy; Prenatal diagnosis; Chromosome microarray

OP8- Chromosome 16q22 Fragility in a Male Patient with Azoospermia: A Case Report

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Abstract

Introduction:

Chromosomal abnormalities are a well-recognized cause of infertility, particularly structural rearrangements that affect key genomic regions. The 16q22 locus has been identified as a recurrent breakpoint in individuals with unexplained infertility, suggesting a potential role in reproductive dysfunction. However, the clinical significance and underlying mechanisms of this chromosomal fragility remain poorly understood.

Case Report:

A 44-year-old male was referred for azoospermia. He had one daughter and an eight-year history of secondary infertility. His history included significant weight gain, followed by bariatric surgery. Comorbidities included diabetes, hypertension, obstructive sleep apnea, and hypercholesterolemia. Family history revealed consanguinity and infertility among relatives. Physical examination noted deep-set eyes, long face, and seborrheic dermatitis. Hormonal evaluation showed normal FSH, borderline elevated LH, and prolactin. Scrotal and abdominal ultrasonography were unremarkable. Semen analysis confirmed azoospermia. Karyotype analysis identified chromosomal fragility at 16q22 in 10% of metaphases. Y-chromosome microdeletion testing was negative. Parental karyotyping was planned to explore potential inheritance.

Conclusion:

Although 16q22 is a common fragile site and may appear in otherwise healthy individuals, its presence has been associated with sperm anomalies and secondary infertility in the literature. This case supports the potential contribution of 16q22 fragility to male reproductive dysfunction and underscores the need for further studies to clarify its role in infertility. The detection of fragility in the parents, together with literature suggesting potential heritability, highlights the importance of clinically evaluating family members as part of a comprehensive assessment.

OP9- Severe Phenotype in Lodder-Merla Syndrome Linked to Homozygous *GNB5* c.863G>A Variant: A Case Report

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Background: Lodder-Merla syndrome is an autosomal recessive disorder caused by mutations in the *GNB5* gene, presenting with a broad clinical spectrum from mild neurodevelopmental delay to severe multisystemic involvement. We report a 12-year-old male, born to consanguineous parents, had hypotonia, non-verbal communication, developmental delay, epilepsy, and cerebral palsy. He had a history of neonatal hypotonia, feeding difficulties, and postnatal intensive care, cardiac arrest following a febrile seizure at age 4. MRI revealed leukomalacia, EEG showed abnormalities, and echocardiography indicated minimal aortic insufficiency.

Methods: Genomic alterations were investigated by conventional karyotyping and whole exome sequencing (WES).

Results: Karyotype analysis was normal; however, WES identified a homozygous missense variant in the *GNB5* gene (c.863G>A, p.Arg288Gln). This variant has previously been reported in a single case in a compound heterozygous state and is classified as pathogenic in the ClinVar database. Notably, the previously reported patient exhibited a milder phenotype, with developmental delay, visual and auditory impairments, episodic bradycardia requiring pacemaker implantation, and no documented seizures. In contrast, our patient presented with a significantly more severe clinical course, including early-onset hypotonia, developmental delay, epilepsy, cerebral palsy, and a history of cardiac arrest following febrile seizure.

Conclusions: Our findings suggest that the homozygous GNB5 c.863G>A variant may result in a more severe phenotype compared to the compound heterozygous case, likely due to zygosi-

ty differences and potential modifying factors, emphasizing the complexity of genotype–phenotype correlations and the importance of comprehensive clinical and molecular assessment in rare genetic disorders.

Keywords: Lodder-Merla Syndrome, GNB5 Mutation, Rare Diseases

OP10- Detection of de novo variants in CTNNB1 and NF1 genes in an infant conceived via in vitro fertilization: a case report

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The *CTNNB1* gene encodes β-catenin, which plays critical roles in both the Wnt/β-catenin signaling pathway and in cell-cell adhesion. As a key effector of the Wnt pathway, β-catenin is involved in processes such as embryogenesis, cell proliferation, and differentiation. Germline pathogenic variants in the *CTNNB1* gene have been associated with a neurodevelopmental disorder characterized by intellectual disability, hypotonia, visual defects, and spastic diplegia, and are most often identified as de novo. Moreover, somatic variants in this oncogene have been implicated in malignancies such as colorectal, hepatocellular, and ovarian cancers.

The *NF1* gene encodes neurofibromin, a tumor suppressor protein that negatively regulates the RAS/MAPK signaling pathway, thereby controlling cell proliferation and differentiation. Pathogenic variants in *NF1* are the primary cause of neurofibromatosis type 1, a disorder characterized by café-au-lait spots, neurofibromas, and an increased risk of malignancy. Affected individuals also frequently exhibit learning disabilities and other neurocognitive impairments. Notably, approximately 50% of cases are caused by de novo variants.

In this report, we present a 10-month-old female infant, conceived as a dizygotic twin via in vitro fertilization, in whom clinical exome sequencing revealed de novo variants in both *CTNNB1* and *NF1*. The patient has *NF1* c.3822_3823del p.Phe1275Profs*8 and *CTNNB1* c.1925_1926del p.Glu642Valfs*5 variants. Both variants were confirmed by Sanger sequencing in the parents and the patient. This exceedingly rare co-occurrence raises questions regarding whether in vitro fertilization and its effects on the embryo may contribute to an increased rate of de novo mutations.

Keywords: in vitro fertilization, exome sequencing, de novo, *CTNNB1*, *NF1*

OP11- Diagnostic utility of Oxford Nanopore-based whole exome sequencing in trio analysis for rare genetic disorders

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Abstract

Background: Whole Exome Sequencing (WES) in a trio format—simultaneously analyzing the proband and both biological parents—offers enhanced diagnostic yield in rare and undiagnosed genetic conditions by enabling the detection of *de novo*, inherited, and compound heterozygous mutations. Recent advancements in long-read sequencing, particularly using Oxford Nanopore Technology (ONT), have overcome many limitations of traditional short-read sequencing, especially in repetitive and complex genomic regions.

Material and Methods: This study focuses on nine WES-Trio analyses conducted between November 2024 and May 2025 at the Medical Genetic Diagnostic Laboratory of Near East University Hospital in Cyprus. Genomic DNA was isolated from peripheral blood samples of affected individuals and their parents. Library preparation and sequencing were performed using the WholEx Pro protocol (IVD-CE, 4Bases, Switzerland), optimized for ONT platforms. Long-read capabilities allowed for the detection of single nucleotide variants, insertions/deletions, and structural variants with high resolution.

Results: Pathogenic/ likely pathogenic/ *de novo* homozygous variants were identified in trios, offering direct insights into disease etiology. For example, a de novo *FOXG1* mutation was found in a patient with encephalopathy, consistent with congenital Rett syndrome. Similarly, compound heterozygous variants in *SUMF1* and *SLC3A1* were implicated in neurodegenerative and metabolic phenotypes. Trio analysis proved especially useful in distinguishing inherited versus *de novo* variants, aiding accurate clinical interpretation.

Conclusion: ONT-based WES-Trio analysis provides a powerful diagnostic tool for complex and rare genetic disorders. Its ability to resolve challenging genomic regions and provide real-time, high-throughput sequencing makes it especially valuable in clinical settings. The application of this approach in our cohort successfully identified causative variants in multiple patients, underscoring the clinical utility of combining LRS with trio-based WES.

Keywords: Whole Exome Sequencing, Trio Analysis, Oxford Nanopore Technology, Rare disease

OP12- Azoospermic Male Case with SRY-Positive 46,XX Testicular DSD

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Abstract:

46,XX testicular disorder of sex development (DSD) is a rare condition characterized by individuals with a female (XX) karyotype presenting with a male phenotype. Here, I present the genetic evaluation of a phenotypically male patient with infertility and a 46,XX karyotype, in whom the SRY gene was detected on the X chromosome.

A 26-year-old male patient presented with infertility. Physical examination revealed bilaterally small testes, with otherwise normal male secondary sexual characteristics. Semen analysis showed azoospermia. Conventional cytogenetic analysis demonstrated a 46,XX karyotype. Y chromosome microdeletion analysis revealed complete deletions in the AZF-a, AZF-b, and AZF-c regions, while the SRY gene was detected as positive. Further analysis using FISH showed localization of the SRY gene on the X chromosome. Based on these findings, the patient was diagnosed with SRY-positive 46,XX testicular DSD.
Patients with SRY-positive 46,XX testicular DSD may present with a normal male phenotype and are often diagnosed during infertility evaluations. This case highlights the importance of comprehensive genetic testing, including the assessment and localization of the SRY gene, in patients with discordance between phenotype and genotype.
Keywords:
46,XX male syndrome; SRY; testicular DSD; infertility; FISH

OP13- Effects of amniotic membrane-conditioned medium on pancreatic cancer cells

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Introduction
The amniotic membrane (AM), a thin layer lining the inner placenta, has gained attention for its unique biological properties, including anti-viral, anti-tumoral, anti-inflammatory, and anti-angiogenic effects. As a biomaterial free of ethical concerns, AM presents promising potential in cancer therapy. This study aims to evaluate the impact of human amniotic membrane-conditioned medium (hAM-CM) on pancreatic cancer (PANC-1) cells, a malignancy with high mortality and limited treatment options.
Materials and Methods
hAM-CM was prepared and applied to PANC-1 and HEK-293 cells. Cell proliferation was assessed using the XTT assay. Migration was evaluated via wound healing assay, while invasion was analyzed using Matrigel-coated inserts. Morphological changes were observed microscopically. Gene expression levels of IL1β, IL-6, IL-17, and HIF1α were measured by qRT-PCR. ELISA was used to quantify total and secreted protein levels of IL-17, HIF1α, and VEGF.
Discussion
hAM-CM significantly reduced the viability, migration, and invasion of PANC-1 cells, with no adverse effects on HEK-293 cells. Gene expression analysis indicated increased expression of inflammation- and hypoxia-related genes in PANC-1 cells post-treatment. ELISA revealed a complex regulation of cytokine and angiogenic protein secretion.
Conclusion
hAM-CM exerts anti-tumoral effects on PANC-1 cells by reducing proliferation, migration, and invasion. These findings suggest that hAM-CM could serve as a potential therapeutic tool in pancreatic cancer treatment, warranting further investigation.
Keywords: Amniotic membrane, gene expression, conditioning medium, pancreatic cancer

OP14- Utilization of RNAseq as a tool to identify the pathogenic nature of a genomic duplication in an individual with Diamond-Blackfan Anemia.

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Abstract
Background: Although the detection of CNVs has become more accessible with widespread usage of microarrays, interpreting their clinical significance remains challenging. One tool to gain further insight on clinically unknown CNVs is RNAseq. Diamond-Blackfan Anemia (DBA) is a ribosomopathy, where most disease-causing variants lead to loss-of-function in Ribosomal Protein (RP) genes. We previously identified an individual with DBA but no pathogenic RP gene variants. He had a *de novo* genomic duplication with unknown clinical significance encompassing chr1[hg38]:78,534,570-94,193,838. In this study, we utilized RNAseq to investigate the potential impact of this duplication on gene expression and identify its pathogenic nature.
Materials&Methods: RNAseq was performed using Illumina Stranded mRNA Prep kit from whole blood samples of unaffected parents and proband. Transcript counts were quantified using Salmon with a custom GENCODE v47 reference transcriptome excluding pseudogenes, differentially expressed genes were identified using DESeq2, and highly-variable immunoglobulin and T-cell receptor genes were removed. Gene set enrichment analyses (GSEA) were performed via DAVID.
Results: The cytoband-specific GSEA revealed a significant enrichment of 1p22.1 band within the duplicated region and it involved 7 genes including *RPL5*. The most significantly upregulated genes in GSEA for molecular function were ribosomal proteins owing to upregulation of 20 ribosome-related genes.
Discussion&Conclusion: RNAseq revealed that the duplicated region is significantly enriched within the upregulated genes, demonstrating the transcriptional consequence of this previously unknown CNV event. Our findings also provide biological insights into the disease pathogenesis demonstrating a significant compensatory upregulation of other ribosomal genes.

Keywords: Diamond-Blackfan Anemia, RNAseq, CNV

OP15- mRNA sequencing of AMPD2 gene proving transcript length change caused by c.353+11C>T novel intronic variant

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Background

A two-year-old female patient was referred to our clinic by her parents, due to speech and gait disturbances, vacant staring, pronounced truncal hypotonia, and spasticity in the extremities. The patient had a history of a complicated delivery resulting in perinatal asphyxia and brachial plexus injury. Electrocardiogram, echocardiogram, and abdominal ultrasound findings were reported as normal. Previously performed spinal muscular atrophy test, chromosomal microarray and karyotype analyses yielded normal results. On clinical examination, facial dysmorphic features included: prominently low-set ears, strabismus, downslanting palpebral fissures, micrognathia, and tapering fingers.

Methods:

Trio whole-exome sequencing (WES) was performed using DNA samples obtained from the patient and her parents. Analysis revealed a homozygous variant in the AMPD2 gene (NM_001368809.2) c.353+11C>T, with both parents identified as heterozygous carriers. The phenotype was found to be partially consistent with pontocerebellar hypoplasia type 9 (PCH9), a condition associated with AMPD2, which typically manifests more prominently at older ages. The variant was suspected to create a novel splicing site; therefore, blood samples were collected from the patient and her parents for RNA extraction. Subsequent cDNA analysis via gel electrophoresis and Sanger sequencing confirmed the presence of an alternative splicing event.

Conclusions:

This study designates the early-onset phenotype of PCH9 in a female patient carrying a splicing-altering variant in AMPD2. It also highlights the feasibility of functional studies in evaluating intronic variants. Functional validation of such variants, can provide insights for clinical decision-making for the patient and further reproductive planning for the family.

OP16- SCITUNA: Single-Cell data integration tool using network alignment

Aissa Houdjedj, Yacine Marouf, Mekan Myradov, Süleyman Onur Doğan, Burak Onur Erten, Oznur Tastan, Cesim Erten and Hilal Kazan

Abstract

Background: As single-cell genomics experiments increase in complexity and scale, the need to integrate multiple datasets has grown. Such integration enhances cellular feature identification by leveraging larger data volumes.

However, batch effects—technical variations arising from differences in labs, times, or protocols—pose a significant challenge. Despite numerous proposed batch correction methods, many still have limitations, such as outputting only dimension-reduced data, relying on computationally intensive models, or results in overcorrection for batches with diverse cell type composition.

Results: We introduce a novel method for batch effect correction named SCITUNA, a Single-Cell data Integration Tool Using Network Alignment. We perform evaluations on 39 individual batches from four real datasets and a simulated dataset, which include both scRNA-seq and scATAC-seq datasets, spanning multiple organisms and tissues. A thorough comparison of existing batch correction methods using 13 metrics reveals that SCITUNA outperforms current approaches and is successful at preserving biological signals present in the original data. In particular, SCITUNA shows a better performance than the current methods in all the comparisons except for multiple batch integration of lung dataset where the difference is 0.004.

Conclusion: SCITUNA effectively removes batch effects while retaining the biological signals present in the data. Our extensive experiments reveal that SCITUNA will be a valuable tool for diverse integration tasks.

Keywords: Single-cell data integration, Batch effect, Rare cell types, Iterative correction.

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OP17- Integrated Trio Phasing from BAM Files for Enhanced Clinical and Research Applications

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Introduction

Parent-of-origin haplotype reconstruction is vital in medical genetics—for diagnosing imprinting disorders, resolving compound heterozygosity, mapping runs of homozygosity (ROH) and copy-neutral loss of heterozygosity (CN-LOH)—and underlies allele-specific expression, population genetics, genotype imputation, pharmacogenomics, and preimplantation genetic testing.

Methods

A Python/C++ pipeline ingests aligned trio BAM files directly, converts them into a concise ".hap" format capturing consensus nucleotides and base qualities, and arranges data in a Trio Directory Structure. A single linear-time (O(n)) algorithm

then performs metadata parsing, high-confidence allele selection, contig ligation, trio inheritance assignment, and block assembly. Outputs are tab-delimited haplotype blocks annotated with coordinates and parent-of-origin.

Results

Applied to 15 Turkish clinical trios, the method fully reconstructed known maternal and paternal haplotypes across all targeted regions. In two probands with SNP-array–detected ROH, it matched reported intervals and unambiguously assigned parental origin. In two cases with CN-LOH, it correctly identified uniparental segments. Processing scaled linearly: human chromosome 1 (249 Mb) completed in 106 s, chromosomes 21 and 22 (~35 Mb each) in under 150 s.

Discussion

By eliminating VCF dependency, this BAM-centric approach reduces I/O and variant-calling biases. Unlike maximum-likelihood fragment assemblers requiring pre-called variants, it integrates mixed short- and long-read datasets without phase breaks and embeds parent-of-origin assignment within phasing. Rapid, modular outputs facilitate seamless integration into diagnostic and research workflows.

Conclusion

This direct BAM-driven trio phasing method delivers rapid, accurate, and lineage-aware haplotype reconstruction. Verified across 15 clinical trios, its linear scalability and clear outputs suit both medical genetics laboratories and genomic research.

Keywords: haplotype phasing • next-generation sequencing • trio analysis • runs of homozygosity • CN-LOH • clinical genetics

OP18- Expanding the Diagnostic Perspective on the 22q11.2 Critical Region: Analysis of a Case Series of Deletions and Duplications

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Introduction

The 22q11.2 region is a critical genomic area associated with a broad clinical spectrum, including DiGeorge/Velocardiofacial Syndrome (microdeletion) and 22q11.2 Microduplication Syndrome. This region's low copy repeats (LCRs) mediate deletions, duplications, and translocations by promoting genomic instability through non-allelic homologous recombination.

Although microdeletions in the 22q11.2 region are more commonly observed and reported, microduplications and Cat Eye Syndrome (CES) should also be considered in the differential diagnosis due to their phenotypic overlap with 22q11.2 deletion syndrome. These CNVs exhibit significant inter- and intrafamilial clinical variability.

Materials and Methods

This retrospective study includes 7 patients (4 with deletions and 3 with duplications) who underwent clinical and genetic evaluation. Diagnostic analysis involved both FISH and SNP-CMA, which can detect atypical CNVs often missed by conventional FISH probes limited to the LCR22A–B interval. Parental segregation studies were performed in all cases.

Discussion

The observed phenotypic heterogeneity underscores the complexity of 22q11.2 CNVs. Accurate diagnosis requires comprehensive methods capable of detecting atypical CNVs outside classical probe targets. While most CNVs arise de novo, familial inheritance with variable expressivity is not uncommon.This makes parental segregation analysis an indispensable tool for precise genetic counseling and accurate recurrence risk assessment.

Conclusion

Our findings support the need for comprehensive analysis of the 22q11.2 region using both microarray and parental segregation testing to ensure accurate diagnosis, personalized counseling, and effective clinical management, not only for deletions but also for duplications that may present with overlapping phenotypes.

Keywords: 22q11.2 region, LCR, CNV, microarray, FISH

OP19- Cleidocranial Dysplasia Due to *RUNX2* Gross Deletions: Clinical and Molecular Insights

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Abstract

Background:

Cleidocranial dysplasia (CCD) is a rare skeletal disorder characterized by hypoplastic or absent clavicles, delayed closure of cranial sutures, and various dental anomalies. Affected individuals commonly exhibit short stature, hypermobile shoulders, and narrow thorax, while cognitive development remains normal. CCD is mostly caused by single nucleotide variants in *RUNX2* gene. However, heterozygous deletions or duplications are reported rarely, in about 10% of all patients.

Methods:

The study included four patients from two unrelated families presenting clinical features compatible with CCD. Clinical exome sequencing-based copy number variation (CNV) analysis was employed to ascertain the genetic background.

Results:

The first family is included three affected patients. Proband is a 14-year-old male, presented with delayed fontanelle closure, hypoplastic clavicles, dental anomalies, and a family history of CCD. Imaging revealed aplastic clavicles, hypoplastic iliac bones, Erlenmeyer flask deformities of the long bones, and genu valgum. Chromosomal analysis was normal, and CNV analysis identified a heterozygous 16-kb deletion involving exons 3–5 of *RUNX2*.

The second family included only affected child. She was presented with clavicular and parietal bone hypoplasia at newborn. CNV analysis revealed a heterozygous 998 bp deletion covering exon 9 of *RUNX2*.

Conclusion:

In patients clinically diagnosed with CCD in whom no pathogenic variants are identified by standard sequence analysis, deletion/duplication analysis of the RUNX2 gene should be considered to detect exon-level or gross genomic alterations. NGS-based copy number analysis represents a valuable tool for identifying such CNVs and can enhance the diagnostic yield in suspected CCD cases with negative sequencing results.

OP20- CD90 knock-out modulates epithelial–mesenchymal traits and enhances drug response in U-CH1 chordoma cells

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Introduction

Chordoma is a rare and chemoresistant tumor with limited therapeutic options. CD90 (THY1), a glycophosphatidylinositol-anchored surface protein, has been linked to stemness and tumor progression in various cancers, but its function in chordoma remains undefined.

Methods

A CRISPR-Cas9 approach was employed to generate CD90 knockout (KO) U-CH1 chordoma cells, which were confirmed by flow cytometry. The expression of EMT markers was assessed by quantitative reverse transcription polymerase chain reaction (qRT-PCR). The migration and invasion properties of CD90-KO cells were evaluated in transwell assays. Cell cycle distribution and sphere formation were evaluated by flow cytometry and ultra-low attachment culture. Drug sensitivity to metformin, etoposide, cisplatin, and methotrexate was measured using MTS assays. Intracellular reactive oxygen species (ROS) levels and antioxidant gene expression were analyzed by DCFDA staining and qRT-PCR.

Results

The CD90 gene was successfully knocked out with CRISPR-Cas9 technology. The loss of CD90 triggered a spindle-shaped morphology, upregulated EMT transcription factors (SNAIL, SLUG, and TWIST), and enhanced invasiveness, indicating EMT activation. CD90 KO cells exhibited G1 arrest and reduced sphere formation despite increased OCT4 and SOX2 transcripts, suggesting non-canonical stem-like states. Dysregulated redox homeostasis, characterized by elevated basal ROS and differential antioxidant responses, likely underlies the enhanced sensitivity to metformin and etoposide.

Discussion

Collectively, these results demonstrate that CD90 depletion promotes an EMT phenotype with altered cell cycle dynamics and redox imbalance, thereby sensitizing chordoma cells to metformin- and etoposide-induced cytotoxicity. Targeting CD90 may overcome chemoresistance in chordoma.

Keywords: Chordoma; CD90; epithelial–mesenchymal transition; drug sensitivity

First report of germline mosaicism in *ZNF292*-related intellectual disability:

OP21- Expanding the clinical and molecular spectrum

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Background:

Heterozygous pathogenic variants in *ZNF292* are associated with intellectual developmental disorder 64 (#619188), frequently characterized with developmental delay and dysmorphic features. A limited number of cases have been documented, and none of them have indicated germline mosaicism. We aim to expand the clinical and molecular spectrum of the disorder by presenting a case with a novel variant and to report germline mosaicism associated with this gene for the first time, enabling appropriate genetic counseling regarding recurrence risk.

Methods:

This study includes the identification of a mosaic variant with a low allelic fraction in the asymptomatic mother's peripheral blood and buccal swab samples through segregation analysis of a case diagnosed with ZNF292-related intellectual disability using whole exome sequencing.

Results:

The proband is a 12-year-old male, born to non-consanguineous parents, referred due to a mild intellectual disability and dysmorphic facial features. Physical examination revealed hypertelorism, a broad nasal bridge, anteverted and prominent ears, retromicrognathia, and a long, triangular face. Karyotype, *FMR1* gene repeat analysis, and chromosomal microarray were all normal. Whole exome sequencing identified a heterozygous c.1531_1532del variant in *ZNF292* gene. Segregation analysis detected the variant in the unaffected mother with a 16% allelic fraction in both peripheral blood and buccal swab samples. The variant was not present in the healthy sister.

Conclusion:

This case expands the known phenotypic spectrum of *ZNF292*-related intellectual disability and represents the first reported instance of germline mosaicism in this condition. Recognition of mosaic parental transmission is crucial for ac-

curate recurrence risk assessment and genetic counseling.

OP22- Retrotransposon Profiling at CNV Breakpoints in Obese Patients Insights from a Single-Center Study

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Retrotransposons(LINEs,SINEs,LTRs) are mobile genetic elements that can lead to genomic instability by causing structural rearrangements through RNA-mediated retrotransposition. Several studies have shown that retrotransposons are associated with the breakpoints-of-CNVs.Obesity is a global health problem and a complex disease influenced by numerous genetic and environmental factors.There is evidence that retrotransposons,such as the methylation status of LINE-1,may be associated with various phenotypes of obesity and metabolic syndrome.This study aims to investigate the retrotransposon profiles at the breakpoints of CNVs detected in a single-center cohort of obese patients.In our centre,SNP-Microarray analysis was performed on 47 patients diagnosed with obesity.The detected CNVs were analysed for the presence of retrotransposons using the RepeatMasker track in the UCSC Genome Browser.126 CNVs were included as a result of CNV analyses performed in the obese patient cohort.Analysing the retrotransposon profiles at the breakpoints,it was observed that 40 CNVs(31.7%) contained the same type of retrotransposon at both breakpoints.The majority of these(87.5%) were associated with the LINE-1.Our findings suggest a significant proportion of CNVs seen in obese patients may be associated with retrotransposons.Furthermore,studies showing that epigenetic regulation of retrotransposons is associated with obesity that these elements not only contribute to structural variations but may also play a potential role in the complex pathogenesis of obesity.The findings of this study may represent an important step towards understanding genomic instability and structural variations in obesity.Further studies involving larger cohorts are needed to elucidate the mechanisms underlying this association,to clarify the specific role-of-retrotransposons in obesity-associated genomic alterations,to understand their potential implications in clinical genetics.

Keywords: CNV, Breakpoint, Obesity, Retrotransposon, LINE-1

OP23- A Previously Unreported Occurrence of an Ultra-Rare Disease: Intragenic Homozygous Deletion in the *AAAS* Gene

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Introduction: Structural variants of the human genome that are larger than 50 base pairs are defined as Copy-Number-Variants(CNVs). In routine practice, microarrays are often used as the primary technique for genome-wide CNV detection. Advances in microarray technology have improved resolution, enabling identification of previously undetectable CNVs.
Materials/Methods: An 8-year-old male patient, born to consanguineous parents, presenting with adrenal failure, seizures, and swallowing difficulties was referred to the medical genetics clinic. The onset of symptoms was 4 years ago and had been initially evaluated by pediatric gastroenterology and endocrinology with the preliminary diagnosis of Triple A/Allgrove syndrome(TAS). Upon examination, hyperpigmentation, gait disturbance and mild facial dysmorphism were observed. Previous laboratory tests revealed elevated ACTH and low cortisol levels, indicating adrenal insufficiency. Endoscopic, manometric and radiologic findings were consistent with achalasia, and Schirmer test revealed dry eyes. Considering the multiple anomalies, and to assess both loss-of-heterozygosity regions and the degree of consanguinity, SNP-microarray was performed.
Discussion: SNP-microarray detected a 6kb homozygous deletion in 12q13.13 with both breakpoints within *AAAS* gene, removing exons 3-7. Although the CNV appears to be in-frame, the lack of healthy population data, variant removing >10% of the protein, and the highly-specific phenotype increases the pathogenicity.
Conclusion: With an estimated prevalence of <1/1000000, Allgrove syndrome is an ultra-rare disorder. This case represents the first report of an intragenic homozygous deletion in *AAAS* gene, expanding the molecular spectrum of TAS and highlighting the utility of SNP-microarray in detecting small, clinically significant CNVs.

Keywords: Triple A/Allgrove Syndrome, AAAS, Microarray, CNV

OP24- Unraveling blended phenotypes: A pediatric case with dual *de novo* variants in *NSD1* and *TAB2*

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Introduction:

Dual molecular diagnoses, though rare, are increasingly recognized in pediatric genetics due to advances in next-generation sequencing (NGS). These cases often present with complex, overlapping phenotypes that do not compatible with a single syndrome. Here, we report a pediatric patient with a dual molecular diagnosis confirmed by whole exome sequencing (WES), highlighting the diagnostic power of NGS in elucidating blended phenotypes.

Methods:

Whole exome sequencing was performed in a pediatric patient presented with a complex clinical presentation. No single preliminary diagnosis could be considered via clinical evaluation before molecular analysis. Detected variants were evaluated based on ACMG/AMP guidelines, and familial segregation analysis was conducted to assess inheritance patterns.

Results:

A 5-month-old male, born to non-consanguineous parents, was referred from the neonatal intensive care unit due to cardiomyopathy and dysmorphic facial features. Physical examination revealed dolichocephaly, frontotemporal balding, frontal bossing, thin lips, large posteriorly rotated ears, inguinal hernia, velvety and lax skin, and joint hypermobility. Growth parameters were within normal limits, but he presented with marked hypotonia and global developmental delay. Echocardiography showed both ASD and VSD. Whole exome sequencing identified two *de novo* pathogenic variants: *NSD1*:c.4875_4878del, associated with Sotos syndrome, explaining the dysmorphic features and neurologic involvement; and *TAB2*:c.445del, associated with congenital heart defects, multiple types, 2, explaining the connective tissue abnormalities.

Conclusion:

This case illustrates the value of considering dual molecular diagnoses in patients with atypical or overlapping phenotypes. Comprehensive genomic analysis, such as WES, can uncover coexisting rare conditions, enabling accurate diagnosis and more informed clinical management.

OP25- A novel inframe CREBBP mutation in a cohort of three pa-tients with Rubinstein-Taybi syndrome

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Introduction:

Rubinstein-Taybi syndrome (RTS) is a rare genetic disorder characterized by intellectual disability, postna-tal growth retardation, microcephaly, distinctive facial dysmorphism, broad thumbs and toes. The genetic basis of the syndrome is largely attributed to mutations in the CREBBP gene, accounting for up to 55% of cases, while mutations in the EP300 gene are responsible for a smaller proportion (~8%).

Method:

After obtaining a comprehensive medical history, constructing a pedigree, and performing a thorough clini-cal evaluation, DNA was isolated from peripheral blood samples of the patients using Zeesan Lab-Aid 824s Blood Isolation Kit. The SOPHIATM Clinical Exome Solution (CES) V2 next generation sequencing kit cov-ering 5400 genes and Illumina NovaSeq system were used for DNA sequencing.

Case:

Of the three patients who presented with dysmorphic features, including broad thumbs and toes, polydac-tyly, and syndactyly, two were male and one was female. All three patients showed delayed motor mile-stones. Both male patients had cryptorchidism. Genetic analysis identified a novel in-frame c.3998_4006del (p.Arg1333_Gly1335del) variant located in exon 24 of the CREBBP gene, as well as the previously reported c.3832G>A (p.Glu1278Lys) and c.1943dupC (p.Ala649Serfs*39) variants, respectively. The patient carry-ing the c.3998_4006del variant had agenesis of the corpus callosum. The patient with the c.3832G>A vari-ant presented with growth retardation and persistent diarrhea during the first year of life.

Results:

In this study, the clinical features and genetic findings of three patients diagnosed with RTS were evaluated, and a novel mutation identified in one of the cases contributed to the existing literature.

Keywords: Rubinstein-Taybi syndrome (RTS), CREBBP, inframe novel mutation

OP26- ReNU Syndrome A Newly Discovered Prevalent Neurodevelopmental Disorder

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Introduction: ReNU syndrome (RS, *RNU4-2*-related neurodevelopmental disorder) is a recently defined monogenic

condition characterized by facial dysmorphism, microcephaly, hypotonia, global developmental delay (GDD), intellectual disability, epilepsy, and multisystem involvement. Pathogenic variants in the non-coding *RNU4-2* gene, encoding U4 small nuclear RNA (snRNA), a core spliceosomal component, have been identified in ~0.4% of individuals with undiagnosed neurodevelopmental disorders (NDDs). As these variants are not detectable by exome sequencing, phenotypic evaluation and targeted testing are warranted. We report a 3-year 3-month-old girl with features suggestive of RS, diagnosed through *RNU4-2* sequencing. This case underscores the diagnostic relevance of *RNU4-2* testing in unexplained NDDs. As the first confirmed case in our study, it is presented as a preliminary observation.
Materials and Methods: Phenotypic evaluation was performed through manual review of clinical records, focusing on features consistent with RS, using keyword-based screening. Given the phenotypic overlap with RS, *RNU4-2*-specific primers were designed, and Sanger sequencing was performed.

Results: A heterozygous pathogenic variant, *RNU4-2* (NR_003137.3):n.64_65insT, was identified in the patient, confirming the diagnosis of RS. The patient with GDD, microcephaly, hypotonia, facial dysmorphism, gastroesophageal reflux, acrocyanosis, constipation, feeding difficulties, and failure to thrive was retrospectively evaluated.
Discussion: This case represents one of the first confirmed RS diagnoses in Türkiye. As variants in such genes are only detectable by whole genome sequencing—a costly approach—targeted Sanger sequencing in *RNU4-2*–like cases may offer a cost- and labor-effective first step, followed by exome and genome sequencing if negative.
Keywords: GDD, ReNU syndrome, *RNU4-2*, Sanger sequencing

OP27- Angelman Syndrome: The Intersection of Genetic Mechanisms and Neurological Phenotype
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Angelman syndrome is a rare, well-characterized neurogenetic disorder with a defined genetic basis, presenting with developmental delay, speech impairment, ataxia, epilepsy, and a distinctively happy demeanor; additional clinical features include microcephaly, sleep disturbances, hyperactivity. The underlying cause of the syndrome is the loss of maternal expression of the UBE3A gene, located in the 15q11-q13 chromosomal region. This genetic anomaly can result from various mechanisms, including deletion, uniparental disomy, imprinting center defect, or UBE3A mutation.
Materials and Methods:
Data from 11 patients diagnosed with Angelman syndrome and followed at our clinic between 2014 and 2025 were retrospectively analyzed.
Results:
Seven patients (63.6%) were female. The median age at diagnosis was 18 months. All patients were referred due to developmental delay. EEG abnormalities and seizures were identified in 7 patients (63.6%), all of whom were receiving antiepileptic treatment. Diagnosis was established in 3 patients by FISH analysis, in 3 patients by array CGH, in 2 patients by MLPA, and in 3 patients through detection of mutations in the UBE3A gene.

Conclusion:
Most Angelman syndrome cases are diagnosed early due to developmental delay and seizures. Its molecular heterogeneity requires multiple genetic tests for confirmation. Early testing accelerates diagnosis, and identifying the specific genetic cause is key for management and counseling. The syndrome's complexity calls for a multidisciplinary approach.

OP28- All Roads Lead to CYLD: A Familial Brooke-Spiegler Syndrome Case
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The CYLD gene, located on chromosome 16q12.1 encodes a tumor suppressor enzyme that playing a vital role in cell proliferation and apoptosis. Disruption of this pathways can lead to various skin tumors, including cylindromas, trichoepitheliomas and spiroadenomas, commonly seen in Brooke Spiegler Syndrome(BBS).
We evaluated a multigenerational family through clinical assessment and genetic testing. Peripheral blood DNA was analyzed using Next Generation Sequencing(NGS) to detect CYLD gene variants
A 41-year-old female presented with multiple facial and scalp lesions beginning in adolescence. Family history revealed similar findings in her daughter, three sisters and mother. Notably, her brother died of lung cancer at the age of 26 and another daughter was diagnosed with Noonan Syndrome. Genetic testing identified a heterozygous c.850C>T (p.Gln284*) nonsense variant in exon 8 of the CYLD gene and classified as pathogenic according to ACMG guidelines. Segregation analysis confirmed the presence of this variant in other affected family members.
This case highlights the classical triad of Brooke Spiegler Syndrome, with familial clustering and clearly pathogenic variant. While BBS typically manifests with skin tumors the brother's

early-onset lung canser may varrant further investigation of non cutaneous cancer risks .Genetic counseling and dermatological surveillance remain critical for affected families.

Keywords: Brooke Spiegler Sydrome, CYLD gene, Cylindroma, Trichoepithelioma, Familial skin tumors, Lung Cancer

OP29- Detection of Intron 22 Inversion in the F8 Gene Using Oxford Nanopore Long-Read Sequencing

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Abstract:

Intron 22 inversion (Inv22) of the F8 gene is the most common genetic cause of severe Hemophilia A, typically diagnosed using Inverse Shifting-PCR. Comprehensive molecular diagnosis for Hemophilia A currently requires a combination of methods, including PCR for Inv22, MLPA for large deletions/duplications, and either Sanger or next-generation sequencing (NGS) for point mutations. However, this multi-step approach is time-consuming, costly, and often cannot be fully performed at a single center—potentially delaying diagnosis and increasing healthcare burden.

In this early-stage study, we assessed the feasibility of detecting Inv22 using Oxford Nanopore long-read sequencing. Genomic DNA from a single male patient with a known Inv22 was sequenced at low coverage (4–5 reads). Despite the limited read depth, the inversion was clearly detected through long-read alignment. Specifically, soft-clipped reads aligning to intron 22 were observed in IGV, suggesting a breakpoint, and supporting the presence of a structural inversion.

Although not yet ready for routine diagnostics, this result highlights the potential of long-read sequencing to streamline F8 genotyping. A single, scalable assay could detect inversions, deletions, point mutations, and deep intronic variants—many of which are missed by conventional methods. If further optimized for cost, coverage, and analysis pipelines, this approach may offer a comprehensive and accessible alternative for Hemophilia A diagnosis, reducing the need for multiple specialized referrals. These advantages may also extend to other rare diseases with similar mutation profiles, where structural variants play a key pathogenic role.

OP30- Identification of Novel Variants in the Ultra-Rare Hardikar Syndrome: A Case Report

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Introduction

The *MED12* gene is associated with Lujan-Fryns, Ohdo, Opitz-Kaveggia, and Hardikar syndromes (HS). HS is a rare condition with X-linked dominant inheritance. It may include anomalies of the biliary tract, the genitourinary system and congenital heart defects, and distinctive craniofacial features. We report a patient with HS who had a novel intronic deletion and frameshift mutation in the *MED12*.

Case Presentation

She was born to a 20-year-old G1P1 mother at 36 weeks and 4 days of gestation via cesarean section due to bradycardia. Birth weight was 2520 grams. Prenatal ultrasonography (USG) revealed tricuspid valve dysplasia, coarctation of the aorta, cleft palate-lip, single umbilical artery, increased echogenicity in the small intestine, and absence of the gallbladder. In the postnatal period, bilateral hydronephrosis, megaureter and anterior ectopic anus were detected. Liver biopsy revealed cholestatic type injury findings and fibrotic enlargement in portal areas. Postnatal USG findings were compatible with biliary atresia. It was learned that she died at the age of 2.5 months after Kasai operation and subsequent liver transplantation from a living donor.

Whole exome sequencing and segregation analysis revealed a de novo *MED12* frameshift mutation, c.1758_1759insTAG (p.Glu587*), and an intronic deletion, c.1745-13_1754del. Visualization in IGV confirmed that the variants were located in cis.

Discussion

Our case, which presented with features of HS and carried two novel variants in the MED12 gene, differed from other reported cases by exhibiting early mortality due to liver failure. In disorders where the same gene is affected can show variable phenotypes, the documentation of novel variants and their clinical consequences plays critical role in refining genotype-phenotype correlations.

Keywords: Hardikar Syndrome, MED12, Biliary atresia

OP31- Coffin-Siris syndrome with clinical and genetic features: case series

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Key Words: Coffin Siris Syndrome, Intellectual disability, ARID1B

Introduction: Coffin-Siris syndrome (CSS) is a congenital syndrome characterised by growth retardation, coarse face, aplasia/hypoplasia of the distal phalanx or nail, hirsutism/hypertrichosis and hypotonia. Approximately 200 patients with molecularly confirmed diagnosis have been reported. Heterozygous pathogenic variants in ARID1A, ARID1B, ARID2, BICRA, DPF2, SMARCA4, SMARCB1, SMARCC2, SMARCD1, SMARCE1, SOX11 and SOX4 genes have been associated with CSS. We aimed to present the clinical and genetic features of six cases with pathogenic variants in ARID1A, ARID1B, DPF2 and SMARCC2 genes.
Method: In this study, after isolation of DNA from peripheral blood for genetic testing from patients with CSS ,sequencing was performed with the next generation sequencing method (Illumina, NovaSeq) using QIAseq human exome and SOPHIA TM Clinical Exome Solution(CES) V3 kit.
Results: Of the six patients included in this study, four were boys and two were girls and their ages ranged between 5-20 years. Six different variations were found in the cases, three of which were novel (ARID1B c.1719_1720insA, ARID1B c.5704A>T, ARID1A c.3540-1G>C) and three of which were previously associated with CSS (SMARCC2 c.574C>T, ARID1B c.6880C>T, DPF2 c.1067G>C).
Discussion: CSS is a rare congenital syndrome with high heterogeneity in both genotype and phenotype and the clinical course may be highly variable. Molecular genetic diagnosis is important for the patient and family to receive genetic counselling and clinical management. This study is presented because it contributes to the literature in terms of genotype-phenotype correlation by expanding the genotypic spectrum with new variants.

OP32- Regulation of miRNA in high fat diet induced obesity hypoventilation syndrome

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Obesity has become a major public health problem in recent years. In addition to metabolic diseases resulting from obesity, conditions affecting ventilation due to obesity have also increased. The most important of these is obesity hypoventilation syndrome (OHS), which is associated with insufficient oxygen supply to tissues. Expressions in hypoxia-induced factors (HIFs) are the precursor genes for this condition. HIFs are key molecules that regulate how cells respond to inflammation and low oxygen. Evidence suggests that they also play a role in obesity and metabolic diseases. HIF-1α is crucial for maintaining oxygen homeostasis and regulating biological processes, including protein translation, gene transcription, glucose, and energy metabolism. This study aimed to identify HIF-1α-regulated miRNAs in OHS. Recent studies have demonstrated the critical roles of endogenous microRNAs (miRNAs) in regulating gene expression in response to hypoxia. In our study, C57BL/6 mice were divided into HFD (high-fat diet) and ND (normal diet). These groups were divided into the control and adenosine 2A receptor antagonist (istradefylline (IST)) groups. The medulla oblongata tissues of these groups were analyzed by real-time PCR analysis for miR-421 and miR-101a targeting the HIF-1α gene. As a result, miR-101a expression was significantly increased in the HFD_IST group compared to the ND_CON group. The present data support the idea that miRNA might play an important role in obesity and hypoxia.
Keywords: Obesity, Hypoxia, miRNA

OP33- Uncovering inherited hyperlipidemia: The role of genetic testing in early diagnosis and cardiovascular risk reduction

Esra Çelik, Mehmet Kocabey, Ayfer Ülgenalp, Ahmet Okay Çağlayan

Introduction-Aim: Hyperlipidemia is a major risk factor for atherosclerotic cardiovascular disease and the early diagnosis of genetically inherited forms is crucial for reducing morbidity and improving clinical outcomes. This study aimed to evaluate the diagnostic yield and clinical implications of genetic screening in patients diagnosed with hyperlipidemia.
Materials-Methods: Between 2018 and 2025, a targeted next-generation sequencing (NGS) panel encompassing 18 genes associated with lipid metabolism was performed on 106 patients diagnosed with hyperlipidemia who presented to our center. Identified variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG) guidelines. Clinical data were retrospectively reviewed from patient records.
Results: Pathogenic or likely pathogenic variants were detected in 47 patients (44.3%). The distribution of these variants was as follows: *LDLR* (n=33), *LPL* (n=5), *APOB* (n=4), *APOE* (n=3), *PCSK9* (n=1) and *APOC2* (n=1). Notably, 21 of the variant-positive individuals were under 18 years of age, underscoring the critical importance of early genetic diagnosis in pediatric cases.
Conclusion: Our study highlights the dominant role of the *LDLR* gene in the etiology of hyperlipidemia, while also demonstrating that panel-based genetic screening can uncover rare genetic causes. These findings emphasize the importance of genetic evaluation for early diagnosis and family screening, especially in pediatric patients.
Keywords: Hyperlipidemia, NGS, ACMG, *LDLR*, *APOB*

OP34- Prevalence and spectrum of multiple pathogenic variants identified through hereditary cancer panel testing in a cohort of 1,977 patients

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From 2018 to 2025, hereditary cancer panel testing was performed on patients (n=1977) referred to our clinic for various clinical indications. Multiple pathogenic variants were identified in 29 (1.4%) of these individuals.

Heterozygous pathogenic variants were detected regardless of the indication for testing. The most frequently affected genes were *MUTYH* (n=11), *CHEK2* (n=8), *BRCA1* (n=6), and *BRCA2* (n=6). Less frequently, variants were detected in *PALB2, NBN, ATM, RAD51D, BRIP1, NF1, MSH2, MLH1, MSH6, RAD50, TP53, BLM, MPL, BARD1, NTHL1*, and *STK11.*

The most common indications for referral included breast cancer, ovarian cancer, and a positive family history of cancer. Less frequently, patients were referred due to preliminary diagnoses such as neurofibromatosis, colorectal cancer, prostate cancer, gastric cancer, endometrial cancer, lung cancer, and Peutz-Jeghers syndrome.

These findings indicate that the co-occurrence of multiple pathogenic variants in hereditary cancer screening may be more frequent than previously recognized, in line with recent studies reporting dual or multilocus variants carriage in up to 2–5% of patients undergoing multigene panel testing.

Importantly, the identification of multiple genetic etiologies within a single patient highlights the complexity and heterogeneity of hereditary cancer syndromes. This supports the need for a comprehensive, multidisciplinary approach encompassing clinical genetics, molecular diagnostics, risk assessment, and genetic counseling to ensure accurate interpretation and appropriate clinical management.

In conclusion, these results underscore the clinical relevance of extended multigene panel testing and the importance of considering combinatorial genetic risk in the evaluation of patients with hereditary cancer predisposition.

Keywords: cancer, multiple, *MUTYH, CHEK2, BRCA1*

OP35- A case suspected of KBG syndrome, a novel pathogenic variant detected in SETD5

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Introduction: SETD5 is a methyltransferase that targets histone H3K36 for trimethylation and thereby is involved in development of neural progenitors and their derivatives. SETD5-related neurodevelopmental disorder is an autosomal dominant disorder that includes facial dysmorphism, impaired moderate to severe intellectual development and predisposition to moyamoya disease. This study reveals a novel SETD5 pathogenic variant in a KBG syndrome suspected case.

Materials and Methods: Whole exome sequencing (WES) utilized by Next Generation Sequencing (NGS). Family segregation analysis of the identified variant was performed using Sanger sequencing.

Results: Our patient was a 5 years old male. He was born to nonconsanguineous parents and no similar cases were reported in the family. On physical examination short stature, triangular face, prominent nasal bridge, hypertelorism, long and flat philtrum, thin vermilion of the upper lip, retrognathia, macrodontia, crowded teeth, preauricular skin tag, mild brachidactyly, single palmar crease of both hands, unilateral operated polydactyly scar, proximally placed thumbs were detected. Cerebral venous malformation was detected in cranial MRI. Karyotype and array analyses were normal. Based on dysmorphic facial features, KBG syndrome was suspected. However, no pathogenic variants were found in ANKRD11 gene. Eventually we detected SETD5 c.2120G>A (p.Trp707*) pathogenic novel variant in WES analysis. Family segregation analysis confirmed that the variant occurred de novo.

Discussion: This study highlights the need to consider SETD5 mutations in patients with KBG-like facial features but without ANKRD11 variants, and underlines distinguishing clinical signs between SETD5-related neurodevelopmental disorder and KBG syndrome.

Keywords: SETD5, Neurodevelopmental disorder, Dysmorphism, KBG syndrome

OP36- A novel splicing variant in *RORB* in a patient with epilepsy

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Introduction: RAR-related orphan receptor beta is a nuclear receptor and a transcription factor encoded by *RORB*. *RORB* is predominantly expressed in central nervous system, particularly in regions related with circadian rhythm. Pathogenic variants in *RORB* have recently been associated with susceptibility to idiopathic generalized epilepsy. In the largest available cohort of cases with RORB related disorder, the most common seizure type is absence seizure. More than half of the patients also have variable degrees of intellectual disability.

Case presentation: We report a 14 year-old male patient with epilepsy. His first seizure was at 2 years old. The patient's early developmental milestones were according to his age and he had no major congenital anomalies, dysmorphic features, or intellectual disability. His father's grandmother and his mother's cousin had history of seizures. EEG studies revealed epileptiform abnormalities. Patient's seizures were mostly generalized tonic-clonic type. The seizures were resistant to levatiracetam and were controlled with valproic acid.

We performed whole exome sequencing to enlighten the molecular etiology behind the seizures. We identified c.93+1G>T variant in *RORB* at heterozygous state (NM_006914.4). The variant was absent in healthy controls and is expected to disrupt splicing. We classified the variant as likely pathogenic according to the ACMG criteria.

Conclusion: We report a novel variant in *RORB*, an ultra rare cause of epilepsy, highlighting the importance of exome sequencing. Our case also represents a relatively uncommon presentation of RORB related disorder regarding the seizure type and normal intellectual development.

Keywords: RORB, epilepsy, next-generation sequencing

OP37- A novel variant in the *COASY* Gene: A case with arthrogryposis and pontocerebellar hypoplasia

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The *COASY* gene encodes an enzyme involved in the biosynthesis of coenzyme A. Biallelic pathogenic variants in this gene are responsible for two distinct phenotypes: COASY protein-associated neurodegeneration(CoPAN) and pontocerebellar hypoplasia type 12(PCH12). PCH12 is characterized by neonatal respiratory failure, microcephaly, arthrogryposis, and pontocerebellar hypoplasia. Here, we present a case with a novel homozygous variant in the *COASY* gene associated with PCH12; a rare, perinatal-lethal neurodegenerative disorder.

A week-old female patient was referred to the Medical Genetics department with findings of dysmorphic features, respiratory distress, and multiple joint contractures. Clinical evaluation revealed microcephaly, hypertelorism, broad nasal bridge, clubfoot, and arthrogryposis. She also had lissencephaly and cerebellar hypoplasia. The parents were consanguineous and had previously lost a child with skeletal malformations. The patient's karyogram, SNP-array analysis, and FISH testing for Miller-Dieker syndrome were normal. A comprehensive NGS panel(KAPA HyperCap Heredity) was performed and revealed a homozygous missense variation in the *COASY* gene(ENST00000590958, c.1177A>C). Both parents were observed to harbour the same variant, heterozygously. The proband was deceased in 10 months.

Detected missense change was not reported in the literature before. It was not found in population databases(ACMG criteria PM2). *In silico* tools predicted the variant to disrupt the protein structure and/or function(PP3). The clinical features of the proband were found to be fully compatible with the *COASY*-related phenotype(PP4). Only a few patients with PCH12 have been reported, making this case clinically noteworthy. Since pontocerebellar hypoplasia is genetically heterogeneous, evaluation with comprehensive molecular panels is crucial in establishing a definitive diagnosis.

Keywords: *COASY*, Coenzyme A Synthase, pontocerebellar hypoplasia, arthrogryposis

OP38- Targeted effects of Intronistat B on PLD1 and PLD2: an in silico and in vitro approach in glioblastoma cells

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Introduction: Glioblastoma multiforme (GBM) is the most aggressive primary brain tumor, characterized by its invasive nature and resistance to conventional therapies. HIF1A and PLD2 from the phospholipase family play critical roles in glioblastoma progression. According to Protein Atlas data, the expression of these genes is increased in glioblastoma cells, supporting their survival, metastasis, and angiogenesis capabilities.

Materials and Methods: This study aimed to evaluate the binding potential of Intronistat B to HIF1A and PLD2 via in silico docking, guiding subsequent in vitro validation in GBM models. For protein targets, PDB structures 3KCX for HIF1A and 6OHP for PLD2 were utilized. Active sites were defined as pocket ID:1 (volume: 1068 $Å^3$) and the catalytic domain, respectively. The 3D structure and SMILES code of Intronistat B were obtained from the PubChem database. In docking analyses performed using the CB-Dock2 platform, binding scores of -8.5 kcal/mol for HIF1A (3KCX) and > -7.0 kcal/mol for PLD2 (6OHP) were obtained.

Discussion: Docking analyses revealed that Intronistat B exhibited high binding affinity to both target proteins. The binding pockets overlapped with functionally active regions, indicating a probable inhibitory effect. These findings suggest that Intronistat B may interact with residues critical for enzymatic or transcriptional activity, potentially altering tumor progression pathways.

Conclusion: Computer-aided analyses of Intronistat B indicate its potential to exert antitumor effects in glioblastoma cells by suppressing HIF1A and PLD2. If validated by laboratory tests,

this molecule could emerge as a promising drug candidate for glioblastoma treatment.

Keywords: Intronistat B, HIF1A, PLD2, Glioblastoma, Docking

OP39- Homozygous Null Variation in the KIFBP gene: A rare case of Goldberg-Shprintzen Syndrome

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Goldberg-Shprintzen syndrome (GOSHS) is a rare multisystemic genetic disorder characterized by delayed motor and cognitive milestones, distinctive craniofacial dysmorphisms, cardiovascular anomalies, and various musculoskeletal abnormalities. Here, we present a case with a homozygous *KIFBP* gene variant, aiming to underscore the utility of comprehensive genetic panels in diagnosing complex multisystemic disorders.

A 17-year-old female was referred to the Department of Medical Genetics due to dysmorphic facial features, delayed motor milestones, and skeletal abnormalities including scoliosis, pectus excavatum, kyphosis, developmental hip dysplasia, and pes cavus. In the neonatal period, she underwent surgical correction for an atrial septal defect and Hirschsprung disease. Clinical evaluation revealed a failure to thrive, microcephaly, and dysmorphic facial appearance with a flat forehead, high-arched eyebrows, upslanting palpebral fissures, blue sclera, convex nasal bridge, and prominent long nose. A comprehensive NGS panel (KAPA HyperCap Heredity) was performed and identified a homozygous variant in the *KIFBP* gene (ENST00000361983, c.169G>T), establishing the diagnosis of Goldberg-Shprintzen syndrome. The variant was a null change resulting in a premature stop codon. It was not found in population databases and has not been previously reported. According to the ACMG criteria, the variant was interpreted as likely pathogenic (PVS1, PM2).

This case with GOSHS enriches the limited literature on this rare condition by broadening its phenotypic spectrum and highlights the critical role of molecular diagnostics in the evaluation of complex multisystemic disorders. Reporting such cases aims to raise clinical awareness and facilitate early and accurate diagnosis for affected individuals.

Keywords: Goldberg-Shprintzen syndrome, GOSHS, *KIPBP*, NGS

OP40- OncoSemScore: Integrative Semantic Scoring of Multigenic Co-Occurrences in Hereditary Cancer

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Introduction: Hereditary cancers are among the primary focuses of genetic research and clinical practice. While some of these cancers follow a monogenic inheritance pattern, many exhibit a complex multigenic architecture. However, current algorithms are insufficient to fully explain this intricate genetic structure. Therefore, there is a pressing need for novel mathematical and computational approaches to more accurately analyze hereditary cancer susceptibility.

Material-Methods: We obtained data on 4302 hereditary cancer patients between 2023 and 2025. First, we selected 59 genes among the 5000 that may be associated with hereditary cancer. In the second stage, we identified genes that appear together. We classified them according to the five semantic similarity algorithms. We adapted integrative classifier algorithms developed by Alay MT into classifying semantic similarity algorithms and found a new scoring system.

Results: The co-occurrence probability for both BRCA2–FANCA and ATM–BRCA2 gene pairs was calculated at 18,56%, indicating a comparable frequency of joint occurrence. This similarity reflects their collaborative roles in DNA repair pathways, with BRCA2 and FANCA participating in homologous recombination and the Fanconi anemia pathway, and ATM functioning as a kinase that activates BRCA2 in response to DNA damage.

Discussion: Algorithms on harmony of coexistence of multiple genes are very limited, and the use of new methods developed in cancers with multi-genic inheritance may fulfill a significant need in understanding the co-occurrence rates of genes.

Keywords: Hereditary cancers, semantic similarities, integrative classifier

OP41- A case of Jackson-Weiss syndrome with FGFR1 p.(Pro252Arg) variant: expanding the phenotypic spectrum

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Abstract:

Jackson-Weiss syndrome (JWS) is a rare autosomal dominant disorder characterized by craniosynostosis and foot anomalies, caused by pathogenic variants in the FGFR1 gene. In this case we present a 4-year-old male referred for genetic evaluation due to bilateral toe syndactyly, macrodactyly of the thumbs, and rocker-bottom feet. The patient also had a history of pyloric stenosis that required surgery. Prenatally, polyhydramnios and maternal use of metoclopramide between the 12th and 16th gestational weeks were noted. Postnatal findings included neonatal hypoglycemia and cyanosis. Dysmorphic features included downslanting palpebral fissures, long eyelashes, prominent ears with notched helix, high-arched palate, and syndactyly of the second and third toes. Family history

revealed syndactyly and hearing loss on the paternal side, suggesting autosomal dominant inheritance. Next-generation sequencing identified a heterozygous missense variant in FGFR1: NM_023110.2:c.755C>G (p.Pro252Arg), previously reported as pathogenic. No additional cardiac, auditory, or visual abnormalities were detected.

This case reinforces the clinical relevance of the FGFR1 p.(Pro252Arg) variant and contributes to the growing phenotypic spectrum of JWS. The presence of gastrointestinal findings and detailed family history highlights the importance of considering FGFR1-related syndromes in patients with digital anomalies, even in the absence of craniosynostosis.

Keywords: FGFR1, Jackson-Weiss syndrome, syndactyly, macrodactyly, dysmorphic features

OP42- A case of Jackson-Weiss syndrome with FGFR1 p.(Pro252Arg) variant: expanding the phenotypic spectrum

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Abstract:
Jackson-Weiss syndrome (JWS) is a rare autosomal dominant disorder characterized by craniosynostosis and foot anomalies, caused by pathogenic variants in the FGFR1 gene. In this case we present a 4-year-old male referred for genetic evaluation due to bilateral toe syndactyly, macrodactyly of the thumbs, and rocker-bottom feet. The patient also had a history of pyloric stenosis that required surgery. Prenatally, polyhydramnios and maternal use of metoclopramide between the 12th and 16th gestational weeks were noted. Postnatal findings included neonatal hypoglycemia and cyanosis. Dysmorphic features included downslanting palpebral fissures, long eyelashes, prominent ears with notched helix, high-arched palate, and syndactyly of the second and third toes. Family history revealed syndactyly and hearing loss on the paternal side, suggesting autosomal dominant inheritance. Next-generation sequencing identified a heterozygous missense variant in FGFR1: NM_023110.2:c.755C>G (p.Pro252Arg), previously reported as pathogenic. No additional cardiac, auditory, or visual abnormalities were detected.

This case reinforces the clinical relevance of the FGFR1 p.(kPro252Arg) variant and contributes to the growing phenotypic spectrum of JWS. The presence of gastrointestinal findings and detailed family history highlights the importance of considering FGFR1-related syndromes in patients with digital anomalies, even in the absence of craniosynostosis.

Keywords: FGFR1, Jackson-Weiss syndrome, syndactyly, macrodactyly, dysmorphic features

OP43- A case of 3M syndrome type 2 with a homozygous pathogenic OBSL1 variant: clinical and genetic findings

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Abstract:
3M syndrome is a rare autosomal recessive growth disorder characterized by pre- and postnatal growth retardation, distinctive craniofacial features, and skeletal anomalies. Three genes—**OBSL1**, **CUL7**, and **CCDC8**—have been associated with types 2, 1, and 3, respectively. Here, we report a 15-year-old male with clinical and radiological features consistent with 3M syndrome type 2.

The patient was referred for genetic evaluation due to proportionate short stature and facial dysmorphism. Prenatal ultrasonography showed microcephaly and suspected cerebral anomalies. Postnatal brain MRI revealed polymicrogyria and agenesis of the corpus callosum. Despite normal intelligence (IQ 78), the patient had poor academic performance. Physical findings included triangular face, prominent forehead, deep-set eyes, upslanting palpebral fissures, infraorbital hollowness, zygomatic hypoplasia, and beaked nose. Anthropometric parameters were below the 3rd percentile. Trio-based next-generation sequencing revealed a homozygous frameshift variant in the OBSL1 gene: **c.1273dup (p.Thr425AsnfsTer40)**. Both parents were confirmed as heterozygous carriers.

This case confirms the typical clinical phenotype of 3M syndrome and expands the mutational spectrum of **OBSL1**-related cases. Our findings emphasize the role of targeted genetic testing in patients with syndromic short stature and the importance of integrating clinical, radiological, and genetic data for accurate diagnosis.

Keywords: 3M syndrome, OBSL1, short stature, frameshift mutation, skeletal dysplasia

OP44- Family case report of the m.9185T>C *MT-ATP6* variant highlighting variable expressivity

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Introduction: Mitochondrial disorders frequently demonstrate variable expressivity and incomplete penetrance due to heteroplasmy and tissue-specific vulnerabilities. We report a family carrying the m.9185T>C (p.Leu220Pro) *MT-ATP6* variant with strikingly variable clinical manifestations.

Materials and Methods: The proband is a 16-year-old male

with mild intellectual disability, pes cavus, and EMG-confirmed axonal peripheral neuropathy. Brain MRI and metabolic screenings, including lactate levels were normal. Whole exome sequencing (WES) trio analysis was performed for the proband, which identified the m.9185T>C variant in the *MT-ATP6* gene. This was confirmed by a mitochondrial DNA panel and segregation analysis within the family. His mother exhibited only mild pes cavus without other neurological findings. His maternal uncle presented with progressive axonal and autonomic neuropathy requiring wheelchair dependency, despite no definitive diagnosis after extensive evaluations. The maternal aunt reported mild exercise intolerance, and the maternal grandmother remained completely asymptomatic.

Results: Genetic testing revealed the m.9185T>C (p.Leu220Pro) variant in the *MT-ATP6* gene, as homoplasmic in the proband, his mother, and maternal uncle, while it was heteroplasmic in the maternal aunt (25.5%) and maternal grandmother (58.1%). All family members had normal lactate and blood gas levels.

Discussion: This family illustrates the clinical heterogeneity associated with the m.9185T>C variant in *MT-ATP6*. While the maternal uncle developed severe neuropathy, other carriers, including the homoplasmic mother, remained minimally or entirely asymptomatic. These findings highlight the limited predictive value of heteroplasmy levels alone in mitochondrial diseases.

Conclusion: This case expands the understanding of the m.9185T>C *MT-ATP6* variant, demonstrating variable expressivity and emphasizing the challenges of clinical interpretation in mitochondrial neuropathies.

Keywords: mitochondrial disease, *MT-ATP6*, m.9185T>C, peripheral neuropathy, heteroplasmy, homoplasmy

OP45- A novel variant associated with spastic paraplegia with neurodevelopmental disorder

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Hereditary spastic paraplegia (HSP) is an inherited disorder of the Central Nervous System mainly characterized by gradual spasticity and weakness of the lower limbs. Spastic Paraplegia 56 (SPG56) is a rare autosomal recessive early onset form of HSP. Symptoms include delayed motor development, spastic paraplegia, unsteady gait, and toe walking. Other features are hyperreflexia, and rarely, dystonic posturing or mild cognitive impairment. SPG56 is caused by biallelic pathogenic variants in the CYP2U1 gene, encoding cytochrome P450, family 2, subfamily U, polypeptide 1. In this study, we present a case in which a loss of function variant was detected in the CYP2U1 gene. The proband, a 2-year-old girl, presented with neurodevelopmental delay, inability to walk, hyperactive deep tendon reflexes, and spasticity. She could walk on her tiptoes with assistance, and her speech development was delayed, with an inability to form two-word sentences. In the genetic testing a novel NM_183075 c.615del p.(Tyr205Ter) frameshift homozygous likely pathogenic variant was detected in the CYP2U1 gene (Exon 2). The findings were consistent with Hereditary Spastic Paraplegia. This study presents a novel variant of this rare syndrome.

Keywords: CYP2U1, Spastic Paraplegia 56, autosomal recessive.

OP46- Frank-Ter Haar Syndrome: An uncommon diagnosis revealed by sequencing

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Introduction:

Frank-Ter Haar syndrome (FTHS) is a remarkably rare autosomal recessive disorder characterized by craniofacial dysmorphism, skeletal anomalies, and cardiovascular involvement. It is associated with biallelic pathogenic variants in *SH3PXD2B* gene, which encodes a protein involved in podosome formation, cell adhesion, and migration.

Case Report:

A female neonate born to consanguineous parents was referred to our medical genetics clinic within the first 24 hours of life due to multiple dysmorphic features. Examination revealed hallmark craniofacial anomalies including mild bitemporal narrowing, a wide anterior fontanel (5×2 cm), hypertelorism, low-set ears, nasal bridge hypoplasia, bilateral sandal gaps, and a simian crease on the right palm. Chromosomal microarray analysis was performed as a first-tier diagnostic test and yielded normal results. Subsequent karyotype and next-generation sequencing (NGS) analyses revealed a homozygous c.127C>T (p.Arg43Trp) missense variant in *SH3PXD2B*, confirming the diagnosis of FTHS. The phenotypic findings were consistent with previously described features of the syndrome.

Conclusion:

FTHS is an uncommon genetic condition, with a gradually expanding clinical description based on reported cases. In this case, comprehensive NGS enabled a definitive diagnosis after initial microarray and karyotype analyses yielded inconclusive results. This report highlights the utility of broad NGS panels in evaluating patients with complex phenotypes, particularly in consanguineous populations, and aims to contribute to the limited literature on FTHS.

Keywords: Frank-Ter Haar Syndrome, SH3PXD2B, Next-Generation Sequencing (NGS), Craniofacial Dysmorphism.

OP47- A Case of CTNNB1-Related Neurodevelopmental

Disorder

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Introduction:

The *CTNNB1* gene encodes β-catenin, a protein involved in cell–cell adhesion. β-catenin also plays a crucial role in cell proliferation, differentiation, and developmental processes via the Wnt signaling pathways. While somatic *CTNNB1* variants have been associated with various tumors, in recent years, germline pathogenic variants—particularly de novo truncating and splice-site alterations—have been implicated in a neurodevelopmental disorder known as NEDSDV (MIM 615075). NEDSDV is characterized by microcephaly, intellectual disability, speech impairment, spasticity, and ocular findings. Here, we present a patient referred for neurodevelopmental delay in whom a frameshift variant in the *CTNNB1* gene was detected, leading to a diagnosis of NEDSDV.

Case report:

A 7-year-old female was evaluated for microcephaly, developmental delay, and features of autism spectrum disorder. She exhibited profound developmental delays: head control was achieved at 2 years, independent sitting at 4 years, with no acquisition of walking or speech. Physical examination revealed microcephaly, dysmorphic facial features, spasticity in the lower extremities, and stereotypic movements. Cranial MRI showed delayed myelination; aside from this, no significant pathology was identified in other investigations. Karyotype and chromosomal microarray analyses were normal. Clinical exome sequencing revealed a heterozygous *CTNNB1* c.760del p.(Tyr254Metfs*22) frameshift variant in exon 6, classified as likely pathogenic.

Conclusion:

CTNNB1-related neurodevelopmental disorder was first described in 2012. Since then, over 20 loss-of-function mutations have been reported. We describe a novel, previously unreported frameshift variant predicted to result in protein truncation. The patient's phenotype aligns with known *CTNNB1*-related disorders, contributing to the expanding mutational and clinical spectrum of NEDSDV.

Keywords: *CTNNB1*, NEDSDV, Neurodevelopmental delay.

OP48- A Case of Verloes Bourguignon Syndrome Diagnosed in the Infantile Period

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Introduction

Verloes Bourguignon Syndrome is a rare autosomal recessive genetic disorder caused by homozygous or compound heterozygous mutations in the *LTBP3* gene located on chromosome 11q13. The syndrome is characterized by short stature, amelogenesis imperfecta, maxillary hypoplasia, mandibular prognathism, cardiovascular anomalies, and various skeletal abnormalities. This case report presents a patient with Verloes Bourguignon Syndrome exhibiting distinct clinical features.

Case Report

A 19-month-old male patient was referred to our clinic with a preliminary diagnosis of congenital myasthenia due to prominent unilateral ptosis. Medical history revealed that the patient was born at 41+2 weeks via spontaneous vaginal delivery, with a birth weight of 3050 grams. Notable ptosis of the left eye was observed at birth. The parents were first-degree cousins. Anthropometric measurements included a height of 80 cm (-1.43 SD) and weight of 10 kg (-1.25 SD). Physical examination revealed significant left eyelid ptosis, bilateral puffy upper eyelids, maxillary hypoplasia, Stahl's ear deformity, sparse hair and eyebrows, and yellowish teeth indicative of amelogenesis imperfecta due to enamel absence. Visual tests were normal. Echocardiography (ECHO), electromyography (EMG), and visual evoked potential (VEP) assessments were unremarkable, and cranial MRI and CT showed no abnormalities. Based on these findings, a neuromuscular disease panel was performed.

Results

DNA was extracted from the patient's peripheral blood, and sequencing was performed using the TWIST Custom Select Panel kit on the MGI DNBSEQ-G400 platform. Analysis revealed a homozygous c.3427G>T variant in the *LTBP3* gene, classified as pathogenic according to ACMG guidelines. Based on these findings, the patient was diagnosed with Verloes Bourguignon Syndrome. Parental segregation analysis was planned.

Discussion

This case is noteworthy as a rare presentation of Verloes Bourguignon Syndrome, reflecting its clinical and genetic characteristics. The patient's presentation with ptosis and diagnosis in the infantile period, prior to the development of cardiovascular and dental anomalies, highlights the importance of early diagnosis and follow-up to manage potential complications. This case contributes to the literature by emphasizing the need for early monitoring and appropriate management of this rare syndrome.

Keywords: Verloes Bourguignon Syndrome, *LTBP3*, amelogenesis imperfecta

OP49- A rare case of adult-onset neurodegeneration due to a pathogenic IRF2BPL variant

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Introduction

Neurodevelopmental disorders associated with the IRF2BPL (Interferon Regulatory Factor 2 Binding Protein-Like) gene

are typically characterized by childhood-onset epilepsy, ataxia, speech delay, and motor regression. While pathogenic variants in this gene often present clinically at an early age, adult-onset cases are rare. In this presentation, we report a case of adult-onset neurological decline associated with a stop-gain variant in the IRF2BPL gene.

Materials and Methods

Our case is a 29-year-old male patient referred to us from the neurology outpatient clinic with complaints of progressive walking disturbance and speech slowing over the past 1–2 years.

Initial clinical manifestations began at the age of 24 with a nocturnal seizure, tongue biting, and urinary incontinence, and the patient was diagnosed with epilepsy. Since the age of 26, he developed progressive gait difficulties, speech slowing, and stereotypic movements in the extremities.

For genetic analysis, the Comprehensive Hereditary Panel including the ataxia panel was performed using the KAPA HyperCap Hereditary Panel. Next-generation sequencing (NGS) identified a heterozygous stop-gain variant in the IRF2BPL gene: c.358C>T (p.Arg120*). The variant was classified as pathogenic according to ACMG guidelines and was confirmed by Sanger sequencing. Screening for SCA (spinocerebellar ataxia) trinucleotide repeat expansions yielded normal results.

Discussion

A review of the current literature suggests that heterozygous pathogenic variants in the *IRF2BPL* gene are rare. To date, only 34 such cases have been reported through whole-exome sequencing (WES). Despite the limited number of cases, the associated clinical phenotypes demonstrate considerable variability. These variants are most frequently linked to childhood-onset neurodevelopmental regression. In contrast, the case presented here exhibits a distinct clinical profile, characterized by adult-onset neurological symptoms. This report aims to contribute to the understanding of the phenotypic spectrum associated with pathogenic *IRF2BPL* variants.

Keywords: IRF2BPL, adult onset, ataxia, epilepsy

OP50- KBG Syndrome: A Rare Neurodevelopmental Disorder Characterized by ANKRD11 Loss-of-Function Variants

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Introduction: KBG syndrome is a rare neurodevelopmental syndrome that occurs as a result of loss-of-function variants or deletions involving this region in the ANKRD11 gene located on chromosome 16. ANKRD11 encodes the chromatin coregulator Ankyrin Repeat Domain-Containing Protein 11, which regulates transcription by binding to nuclear receptor complexes in neurons and glial cells. Loss of function of the gene has been associated with phenotypic features such as macrodontia of maxillary central incisors, triangular face, synophrys, hypertelorism, short stature, skeletal anomalies, and brain malformations. The clinical picture is mostly accompanied by feeding problems in infancy, seizures, attention deficit hyperactivity disorder, and learning disabilities.

Case Report: A 10-year-old gril patient was referred to our medical genetics clinic due to attention deficit hyperactivity disorder, heart defect and dysmorphic appearance. As a result of the examination, triangular face, synophrys, brachydactyly was detected in the patient. Karyotype analysis, microarray and NGS analyses were planned for the patient.

Results: Karyotype analysis and microarray results were reported as normal. Next-generation DNA sequencing identified a heterozygous frameshift variant at the c.4411_4412del position in the ANKRD11 gene. According to ACMG guidelines, this variant was classified as Likely Pathogenic, confirming the diagnosis of KBG syndrome (PVS1,PM2).

Conclusion: KBG syndrome is a very rare syndrome and it is important to apply comprehensive gene panels with NGS method in its diagnosis. It is aimed to contribute to the literature in terms of genotype-genotype correlation of KBG syndrome.

Keywords: KBG syndrome, NGS, Macrodontia

OP51- Rare copy number variants of 8p23 gene region and their association with neurodevelopmental disorders

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Introduction: The *8p23* gene region has been implicated in neurodevelopmental disorders (NDDs), yet the clinical significance of rare copy number variants (CNVs) in this region remains poorly understood. This study aims to characterize CNVs in *8p23* and identify novel candidate genes associated with NDDs.

Methods: We analyzed chromosomal microarray data from patients with neuropsychiatric disorders to detect CNVs in the *8p23* region. Clinical findings were correlated with genetic results.

Results: We presented detailed clinical findings of cases carrying heterozygous *8p23* copy number variants. In addition, we identified three novel candidate gene variants of these disorder, following as *TDRP, FAM90A10* and *FAM90A7* genes.

Discussion/Conclusion: Our findings highlight the clinical relevance of *8p23* CNVs in NDDs and propose *TDRP*, *FAM90A10*, and *FAM90A7* as novel candidate genes requiring further investigation. This study underscores the importance of comprehensive CNV analysis for understanding NDD pathogenesis.

Keywords: TDRP, FAM90A10, FAM90A7, 8p23, autism spectrum disorder, intellectual disability

OP52- Single-Center Experience: A Retrospective Evaluation of Prenatal Genetic Counseling and Diagnostic Approach Between January and March 2025

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Background:

Prenatal diagnosis refers to genetic testing used to determine whether a fetus at increased risk for a genetic disorder is affected. This risk may stem from a previous child with a genetic condition, familial disease history, parental carrier status, or high-risk findings in screening.

Prenatal genetic counseling is crucial for early anomaly detection and effective clinical management. Timely, well-indicated testing enhances both clinical outcomes and personalized decision-making.

Material and methods:

This study aimed to evaluate the clinical management of pregnant individuals who underwent invasive prenatal diagnostic testing following referral to our clinic for genetic counseling between January and March 2025. Clinical histories, types of diagnostic tests performed, genetic findings,
and pregnancy outcomes were reviewed using patient records.

Results:

All 33 patients received comprehensive genetic counseling, and non-invasive and/or invasive diagnostic tests were recommended based on case-specific indications. Chromosomal aneuploidy was identified in three cases, and microdeletion/duplication syndromes in three others. Seven patients exhibited copy number variations (CNVs) deemed potentially clinically relevant. One patient was found to carry a familial chromosomal translocation. Additionally, whole-exome sequencing (WES) identified single-gene variants potentially related to the clinical presentation in three cases. Sixteen patients had normal genetic test results. Four pregnancies were electively terminated, while the remaining 29 continued with follow-up or resulted in delivery.

Conclusion:

Our study highlights the critical role of prenatal genetic counseling in multidisciplinary management and the importance of applying diagnostic tests with the correct indications. This comprehensive approach, conducted independently of the referral indication, improves quality and patient compliance in the prenatal diagnosis process and serves as a reference as a single-center experience. As the results of ongoing cases are completed, diagnostic performance will be evaluated through further analysis.

OP53- The effect of early radiotherapy effects on A549 lung cancer stem cell population

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Introduction: Radiotherapy is a commonly used method in the treatment of lung cancer; however, the presence of therapy-resistant cell populations limits its effectiveness. Cancer stem cells (CSC) play a critical role in both tumor recurrence and resistance. This study aimed to investigate the effects of radiotherapy on CSC subpopulations and migration ability in A549 cells.

Material and Methods: A549 cells were irradiated with 0, 2, 4, 6, and 8 Gy. CSC populations were analyzed by flow cytometry at 24 and 48 hours using CD44 and CD24 markers. Cell migration was assessed via scratch assay.

Discussion: Our findings indicate that radiotherapy effect both cell viability and the proportion of cancer stem-like cells in A549 cells in a dose-dependent manner. The most notable reductions were observed at 6 Gy, suggesting this dose may target resistant subpopulation. Decreased migration capacity at higher doses points to a potential anti-metastatic effect of radiation. These results support the therapeutic value of radiotherapy in limiting CSC-related relapses and metastasis.

Results: A significant decrease in cell viability was observed in A549 cells 24 hours after exposure to 2 Gy of radiation, as determined by the MTS assay. Flow cytometric analysis of cancer stem cell populations at 24 and 48 hours revealed dose-dependent variations in the proportions of $CD44^+$ and $CD24^-$ cells. In the 6 Gy group at 24 hours, a significant reduction was detected in both $CD24^-$ (0.54%) and $CD24^-CD44^+$ (2%) cell populations. The migratory capacity of cells was reduced in all groups.

Keywords: Stem cell, radiotherapy, cancer

OP54- Analysis of miRNA Expression Profile by Small RNA Sequencing in Schizophrenia Patients

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Introductıon: This study aimed to analyze miRNA expression profiles and identify potential disease-related biomarkers in schizophrenia patients treated with paliperidone palmitate, a long-acting injectable antipsychotic, using small RNA se-

quencing in peripheral blood.

Materials and Methods: Our study included 20 individuals diagnosed with schizophrenia, 20 individuals diagnosed with schizophrenia and treated with paliperidone palmitate, and 20 healthy control individuals. RNA was isolated from peripheral blood samples collected in EDTA tubes. Following quality and quantity analyses, small RNA sequencing was conducted. For the sequencing process, samples from 3 individuals with schizophrenia, 2 individuals with schizophrenia treated with paliperidone palmitate, and 3 healthy controls were selected. In the bioinformatic analysis, significantly differentially expressed miRNAs were identified based on LogFC, p-value, and FDR (<0.05) criteria.

Discussion: Our results indicate that miRNA expression in peripheral blood is significantly altered in schizophrenia patients. miRNAs such as miR-486 and miR-451a have previously been associated with neuroinflammation, synaptic function, and neuronal plasticity. Although the effect of paliperidone palmitate on these expression profiles is not yet fully understood, the observed changes may be attributed to both disease pathophysiology and treatment effects. Our findings are promising for the discovery of potential diagnostic and prognostic peripheral blood biomarkers in schizophrenia. However, the results need to be validated in larger patient cohorts.

Conclusıon: A total of 15 miRNAs were found to be significantly downregulated in schizophrenia patients compared to the control group. In particular, hsa-miR-486-1/2, hsa-miR-92a-1/2, hsa-miR-451a, and hsa-miR-4732 were found to be noteworthy.

Keywords: Schizophrenia, miRNA, small RNA sequencing, paliperidone palmitate

OP55- Blended RASopathy and autoinflammatory phenotype due to coexisting NF1, RAF1, and MEFV variants: a father–daughter case report

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The RAS/MAPK signaling pathway is a conserved mechanism that regulates cellular responses to growth factors and extracellular stimuli. Genetic alterations in this pathway lead to a group of syndromes known as RASopathies. Among them, Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant neurocutaneous disorders and is usually caused by pathogenic variants in the NF1 gene.

RAF1 is another gene within this pathway. The co-occurrence of NF1 and RAF1 variants in a single individual is rare and may indicate a genetic interaction or modifying effect on phenotype.

Here, we present a proband with a blended phenotype carrying a pathogenic stop-gain NF1 c.4078T>C (p.Gln1360Ter) variant, a stop-gain RAF1 c.874C>T (p.Arg292Ter) variant classified as a variant of uncertain significance (VUS), and a pathogenic missense MEFV c.2177T>C (p.Val726Ala) variant. Clinically, the proband exhibited café-au-lait macules, axillary and inguinal freckling, along with recurrent headaches, dizziness, nausea, and abnormal brain MRI findings. Her father, who was diagnosed following the evaluation of his daughter, showed similar pigmentary findings in addition to multiple neurofibromas.

This case contributes to the understanding of blended phenotypes involving both RASopathy-related and autoinflammatory gene variants. It highlights the importance of comprehensive genetic testing in patients with complex or atypical features. Early and accurate molecular diagnosis is essential for elucidating the underlying genetic etiology, guiding individualized management, preventing potential complications, and enabling long-term follow-up in RASopathies and related conditions.

Keywords: Neurofibromatosis type 1, NF1 gene, RAF1 gene, whole exome sequencing

OP56- Genealogy and ethics after advances in artificial fertilization techniques

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Developments in genetic science and artificial fertilization techniques have brought about many ethical debates. Among these, issues such as cloning, anonymous gamete donation (sperm banking, egg freezing and donation), surrogacy are bioethical issues that also concern biological ties. With these developments, many things about the traditional family structure have changed and the importance of the concept of genealogy/biological ties has been questioned more and more.

Genealogy refers to the biological bond between a person and his/her descendants and ascendants. In Islam, the protection of genealogy, which is referred to as "neseb" in Arabic, has been emphasized and for this reason, it is forbidden for a woman whose husband has died or whose husband has separated from her to marry another man during the 4-month period of iddat to determine whether she is pregnant from her deceased husband. In the Turkish Civil Code, this period is 300 days, except in special cases.

Recently, some researchers have focused on the importance of biological ties in the development of a coherent and positive sense of identity, arguing that an ongoing bond with biological parents is important for self-knowledge and self-formation, and that it is morally wrong to deprive someone of this. This

raises ethically important questions such as whether it is important to know one's biological parents and what kind of value should be attributed to biological ties/ancestry.
This study aims to evaluate the importance of the concept of geneslogy and bioethical issues related to genetics in this context.
Key words: Genealogy, Bioethics, Artificial fertilization.

OP57- A Rare Genetic Cause of Early Infantile Onset Epilepsy: CSNK2B

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Introduction: Poirier-Bienvenu Neurodevelopmental Syndrome (PBNS) is a rare autosomal dominant genetic disorder caused by mutations in the *CSNK2B* gene. This gene encodes the beta subunit of casein kinase 2 (CK2), an eosinophilic serine/threonine kinase involved in processes such as apoptosis, cell proliferation, DNA damage response, neuronal development, signal transduction, metabolic processes, replication, transcription, and translation. *CSNK2B* is abundantly expressed in the brain, particularly in neurons and neuroepithelial cells, and plays a critical role in neuronal development. The syndrome is characterized by various findings such as neurodevelopmental disorder, intellectual disability, developmental delay, epileptic seizures, and, in some cases, hypotonia.
Case Presentation: In this study, we present a 2.5-month-old male patient affected by PBNS. The patient was referred to pediatric neurology with a preliminary diagnosis of epileptic seizures. His parents were not consanguineous. His measurements were: weight 6.2 kg (-0.08 SDS), height 62.0 cm (0.44 SDS), and head circumference 39.5 cm (-1.03 SDS). Physical examination revealed slanted eyes, prominent ears, thick eyebrows, a 0.5×0.5 cm hyperpigmented lesion on the back, and a Mongolian spot on the gluteus maximus. EEG reported multifocal medium-to-high amplitude sharp slow-wave discharges in the left hemisphere. No pathology was detected in the brain MRI. WES, conducted under the preliminary diagnosis of epilepsy, revealed a heterozygous likely pathogenic frameshift variant, c.438del p.Lys147SerfsTer80, in the *CSNK2B* gene.
Conclusion: There are a limited number of reported cases of PBNS in the literature. We report the first case from Turkey. This study contributes to the clinical and genetic diversity and expands the variant spectrum of PBNS. The identified variant in this case supports loss of function as a common molecular mechanism.
Keywords: *CSNK2B*; Epilepsy; Next-Generation Sequencing; Rare Diseases; Poirier-Bienvenu Neurodevelopmental Syndrome

OP58- The role of clinical and genetic findings in the diagnostic process of disorders of sex development: a current overview with single center experience

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Introduction
Disorders of sex development (DSD) are conditions where chromosomal, gonadal, or anatomical sex is atypical. This study aims to retrospectively evaluate the demographic, clinical, laboratory, and genetic features of patients diagnosed with DSD over the last 15 years in a tertiary pediatric endocrinology center.
Materials and Methods
Patients diagnosed with DSD at Erciyes University Pediatric Endocrinology Department between 2010 and 2025 were included. Data were categorized based on the Chicago Consensus
as sex chromosome DSD, 46 XX DSD, and 46 XY DSD.
Results
A total of 241 patients were included (58.9% female). The most common etiologic group was 46 XY DSD (42.3%), followed by sex chromosome DSD (29.5%) and 46 XX DSD (28.2%). Common presentation symptoms were ambiguous genitalia (22%), short stature (19.5%) and hypospadias (12%). In the 46 XX DSD group, 21-hydroxylase deficiency was the most common diagnosis (64.1%). In 46 XY DSD, androgen receptor mutations, SRD5A2, CYP17A1, and PMKS defects were identified. Turner syndrome was the most frequent sex chromosome anomaly (84.5%).
Discussion and Conclusion
This single-center experience emphasizes the complex and heterogeneous nature of DSD. Contrary to some reports, 46 XY DSD was the most prevalent group. Comprehensive clinical, hormonal, imaging, and genetic evaluations are essential for accurate diagnosis and optimal management of DSD patients.
Keywords: disorders of sex development, clinical findings, genetics

OP59- A New Translocation: t(3;6)(q13.3;q27) in a Case of Recurrent Pregnancy Loss (RPL)

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Introduction: Recurrent pregnancy loss (RPL) is when a woman has three or more consecutive miscarriages. Chromoso-

mal abnormalities are frequently seen in RPL cases.
Material Method: In this case report, a female patient who applied to Erciyes University Medical Genetics Department with the indication of RPL was examined with a chromosome analysis for cytogenetic purposes and a thrombophilia panel for molecular genetics.
Result: As a result of the chromosome analysis, a balanced t(3;6)(q13.3;q27) translocation was detected in the female patient. As a result of the thrombophilia panel, it was determined that she had a homozygous mutation for MTHFR C677T and a heterozygous mutation for PAI-1 4G-5G Variant1. The female patient's father was examined in terms of family segregation and it was observed that her father also had a balanced t(3;6)(q13.3;q27) translocation.
Discussion: Balanced translocation is a type of chromosomal anomaly in which two chromosomes exchange parts but the total amount of genetic material remains the same. Balanced translocations are generally harmless to the carrier. This explains why a woman continues her life as a carrier even though a balanced translocation is transferred from the father to the affected individual. However, when the chromosomes are transferred to the child unbalanced, it can cause RPL. Thrombophilia, or a coagulation disorder, is also seen as one of the most important causes of recurrent miscarriages. It is seen that the genetic anomalies we detected in the patient explain the RPL clinic seen in the patient.
Conclusion: This case report shows the importance of examining the clinic thoroughly and conducting cytogenetic and molecular genetic studies together. Our study makes a new contribution to the literature by detecting the t(3;6)(q13.3;q27) translocation, which has not been reported in the literature.

OP60- From ICD Codes to Rare Disease Genetic Counselling

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Background
Timely genetic-counselling referral remains a bottleneck in diagnosing rare diseases. We asked whether a lightweight model derived solely from routinely entered ICD-10 codes could serve as an instant, high-precision triage tool at the moment a molecular test is ordered.
Methods
The dataset is from Erciyes University Hospitals Health Application and Research Center. Covering all genetic-test accessions at a tertiary pediatric hospital between January 2015 and August 2021 (N = 112 314) were linked to encounter-day M800-M899, D50-D89, C00-C97, U00-U49, Q80-Q99) who also had genetic procedure codes (681*), age and sex. A lasso-penalised logistic regression converted the full code universe (~70 000 strings) into a sparse indicator matrix. The penalty parameter was selected by five-fold cross-validation on 2015-2019 data and temporally validated on 2020-2021 encounters. The primary outcome was the presence of a rare-disease code (Q00–Q99 or D81–D89). Counselling impact was simulated by mapping alerts to existing referral slots.
Results
The lasso retained just 22 non-zero coefficients—18 positive and 4 negative. On the 17 321-encounter validation set the model achieved:
– AUROC = 0.9998 (95 % CI 0.9996–1.000)
– Sensitivity = 0.982, Specificity = 0.960
– Positive predictive value = 0.964, Negative predictive value = 0.998
Prospective implementation would trigger a median 1.8 alerts per clinic day, capturing 98 % of encounters that ultimately returned a pathogenic or likely-pathogenic result while increasing counsellor workload by only 4 %. Large positive weights mapped to primary immunodeficiencies (e.g. D84.9, $\beta = +11.3$) and congenital malformation syndromes (Q87.8, $\beta = +7.8$); acute leukaemia codes carried the strongest negative weights (C91.0, $\beta = -5.7$).
Conclusion
A transparent, 22-term ICD-10 rule transforms routine billing data into real-time counselling action, fast-tracking high-probability rare-disease cases without overwhelming limited genetics resources. External validation and a prospective implementation trial are warranted to confirm generalisability and patient-level benefit.
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POSTER PRESENTATION ABSTRACTS

PP1- Investigation of miR-21, miR-150, miR-155 Expression Levels in Chronic Myeloid Leukemia Patients

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Purpose: In this study, the relationship between CML and the expression levels of miR-21, miR-150, and miR-155, which could be used in the follow-up of CML patients, was investigated.
Materials and Methods: RNA and miRNA were extracted from peripheral blood samples of patient and control samples. Targe-ted miRNA expression levels from cDNA samples were analyzed by real-time PCR method.
Results: miRNA expression level was determined as 1.0 in the control group. In the newly diagnosed group, the mean miR-21 fold change was 0.6, miR-150 fold change was 0.3, and miR-155 fold change was 0.5. fold changes for miR-21, miR-150 and miR-155 were found to be 1.4, 0.5 and 2.4 fold, respectively, in the imatinib treatment group. In the nilotinib treatment group, miR-21 level was 3.5, miR-150 level 0.5, and miR-155 level 4.3. In the dasatinib treatment group, fold change was 0.8 for miR-21, 2.1 for miR-150, and 0.5 for miR-155. The mean miR-21 level was found to be 3.2, miR-150 level 1.0 and miR-155 level 2.8. MiR-150 levels were found to be lower in the newly diagnosed group, imatinib group and nilotinib group than in the control samples. This differen-ce between the new diagnosis group ($p=0.07484$) and the nilotinib group ($p=0.01541$) is statistically significant. No significant difference was found between patients and controls in terms of miR-21 and miR-155 levels.
Conclusion: These results support that miRNA-150 can be used as a parameter in the monitoring of treatment of CML patients and can contribute to the early detection of drug resistance.

PP2- Strategic Early Detection of Urolithiasis Through Blood Metabolite Analysis

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Relevance. Urolithiasis is among the most prevalent urological disorders globally, with regional incidence rates ranging from 7% to 20% (Murushidi et al., 2023; Shatylko et al., 2019). In Kazakhstan and other Central Asian countries, the disease is notably widespread, largely due to climatic conditions, dietary patterns, and genetic predispositions (Kaprin et al., 2022). Recurrence rates are high, with up to 67% of patients experiencing stone formation within five years of the initial episode (Alfimov et al., 2023), highlighting the urgent need for early detection and preventive strategies. The epidemiology of urolithiasis in Kazakhstan reveals distinctive features, including potentially higher prevalence compared to global averages, often attributed to limited public awareness and insufficient preventive measures (Kaprin et al., 2022). Key contributing factors include metabolic disorders such as hyperuricemia and hypercalciuria, which are central to the disease's pathogenesis (Chernenko et al., 2018; Eliseev, 2018). Moreover, urolithiasis is frequently associated with comorbidities like osteoporosis and metabolic syndrome, necessitating an integrated, multidisciplinary approach to management and prevention (Krishtopa et al., 2022; Sharvadze et al., 2017).
Key words: urolithiasis, early detection, prevention, kidney stone, metabolites.
Aim. To develop early diagnostic strategies for urolithiasis aimed at optimizing treatment, prevention, and metaphylaxis by analyzing the spectrum and relative concentrations of key urinary metabolites.
Methods. For sensitive and comprehensive metabolomic profiling, high-performance liquid chromatography (HPLC) was employed due to its efficiency and relatively simple sample preparation. Mass spectrometry was utilized for the identification, characterization, and quantification of proteins and metabolites. Metabolite identification was performed using specialized spectral databases based on fragmentation patterns. The Human Metabolome Database (HMDB), which contains 217,920 annotated metabolite entries detected in human blood, was used to classify metabolites by their concentrations and reference ranges (Wishart et al., 2022).

Results. This study presents findings from high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS), visualized through a Venn diagram to compare the number of detected metabolites in patients with urolithiasis and their healthy relatives. Blood samples from individuals diagnosed with urolithiasis (urolithiasis group) and their unaffected relatives (control group) were collected using the dried blood spot (DBS) method. The initial phase focused on optimizing metabolite extraction conditions from DBS to maximize yield. Specifically, extraction efficiency was assessed at pH 2, 7, and 9 for both groups. Comparative analysis of the metabolomic profiles under different pH conditions revealed distinct metabolite sets between the groups, with Venn diagrams highlighting overlapping and unique features.

The analysis showed that the highest number of metabolites was detected at pH 9. The presence of a substantial set of shared compounds at this pH enables the broadest coverage of the metabolome, facilitating the identification of potential diagnostic biomarkers specific to urolithiasis.

Conclusion. This study highlights key metabolic features of urolithiasis identified through high-performance liquid chromatography and tandem mass spectrometry. The greatest number of metabolites was extracted at pH 9, suggesting a distinct biochemical environment potentially linked to stone formation. Comparative profiling revealed notable differences between patients and healthy relatives, indicating the presence of disease-specific metabolites. Future research will focus on characterizing these biomarkers for early diagnosis and targeted therapy, with special attention to overlapping and unique metabolites as well as those consistently present in affected individuals. The inclusion of healthy relatives offers insight into protective and predisposing metabolic factors, paving the way for improved preventive strategies.

PP3-The influence of ADIPOQ gene polymorphisms and alleles on metabolic syndrome and it is components.

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Introduction

Metabolic syndrome (MetS) is a significant public health issue worldwide. It encompasses a cluster of disorders that collectively increase the risk of developing serious diseases — the likelihood of type 2 diabetes increases fivefold, and the risk of mortality from cardiovascular conditions rises by 2.5 times [1,2]. ADIPOQ gene, is a key protein secreted exclusively by adipocytes and plays an important role in the regulation of metabolic processes [3,4].

Methods

A cross-sectional descriptive study was conducted involving 190 patients. All participants underwent biochemical analysis, assessment of anthropometric parameters, blood pressure measurement, and PCR-RFLP was performed.

Results

The prevalence of genotypes and alleles of the ADIPOQ gene polymorphism was studied. The results of the study showed the following genotype and allele frequencies of the ADIPOQ gene: CC genotype – 48.9%, CG genotype – 37.9%, GG genotype – 11.1%. The frequency of the C allele was 63.9%, and the G allele – 36.1%. A statistically significant direct association was found between ADIPOQ gene genotypes and triglyceride levels ($\chi^2 = 9.29$, $p = 0.014$), as well as between the G allele and the component abdominal obesity ($\chi^2 = 4.34$, $p = 0.034$). No statistically significant associations were found with other components of MetS.

Conclusion

In our study, the G allele was more frequently observed in patients with abdominal obesity. The presence of these polymorphisms may serve as a useful tool for assessing the risk of developing MetS and holds clinical significance for the prevention and treatment of metabolic disorders.

Keywords

ADIPOQ gene polymorphism, metabolic syndrome, abdominal obesity.

PP4- The role of MC4R gene polymorphisms and alleles in metabolic syndrome and it is components

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Introduction

The high prevalence of overweight and obesity is one of the most serious public health problems in the 21st century. The pathogenesis of metastases includes many genetic and acquired factors that fall under the definition of insulin resistance and low-grade chronic inflammation. Over the past decade, advances in single-nucleotide polymorphism genotyping technologies have facilitated genome-wide association studies to identify various risk loci/single-nucleotide polymorphisms associated with an increased risk of obesity and type 2 diabetes mellitus [1,2]. The MC4R gene is known to play a central role in regulating energy and appetite, which leads to better control of obesity [3].

Methods

A cross-sectional descriptive study was conducted involving 190 patients. All participants underwent biochemical analysis, assessment of anthropometric parameters, blood pressure measurement, and PCR-RFLP was performed.

Results

According to the results of the genetic study, the frequency of occurrence of MC4R genotypes and alleles of the gene was: CC genotype - 20.5%, TC genotype – 40%, TT genotype - 33.7%, C allele – 45,1%, T allele – 54,9%. A statistically significant direct relationship was found between MC4R genotypes and

triglyceride levels ($\chi 2$ =8,9, p=0.028). Statistically significant associations were found with all components of the MetS.

Conclusion

The results of our study may help to understand the main genetic variations in this gene for better management of the decline in the development of the components of MetS.

Keywords

MC4R gene polymorphism, metabolic syndrome, abdominal obesity.

PP5- Evaluation of balanced chromosomal aberration frequency in healthy Turkish Cypriot couples

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Background:A chromosomal aberration is a condition involving structural or numerical changes in one or more chromosomes.These abnormalities are a significant genetic factor contributing to reproductive issues. Balanced chromosomal aberrationsspecifically refer to structural changes in chromosomes that maintain the proper amount of genetic material, without any loss orgain. Carriers of balanced translocations often face fertility challenges due to improper chromosome segregation during gameteformation. This can result in implantation failure, miscarriages, or birth disorders. However, these individuals are typicallyhealthy and exhibit no developmental abnormalities, which means they are often unaware of their condition. In contrast,unbalanced chromosomal rearrangements can cause developmental issues or spontaneous pregnancy loss. Balancedtranslocation carriers account for approximately 0.2-0.4% of the general population. The purpose of this study was todetermine the prevalence of balanced translocations in the Turkish Cypriot population.

Material and Methods: The study analyzed 50 healthy Turkish Cypriot couples planning to conceive. Chromosomal analysis wasperformed using G-banding karyotyping to identify potential balanced translocations.

Results: Results revealed that 4% of the participants exhibited chromosomal alterations. The most common aberrationsobserved included inversion 9, balanced translocations between chromosomes 4 and 7, derivative chromosome 22, andtranslocations involving chromosomes 4 and 10.

Conclusion: Cytogenetic analysis of conception products plays a critical role in uncovering the causes of miscarriages. Inconclusion, the frequency of chromosomal alterations found in the Turkish Cypriot population, consisting of 80,000 individuals,represents an important finding. This insight is crucial for family planning considerations and shaping government policies.

Keywords: Balanced translocation, cytogenetics, chromosomal aberrations

PP6- Evaluation of the pathogenicity of variants of uncertain significance in the *BRCA2* gene through ın silico analyses and clinical correlation

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Introductıon:

The *BRCA2* gene plays a key role in DNA repair and tumor suppression, with variants often linked to breast and ovarian cancers. Variants of uncertain significance (VUS) pose challenges in risk assessment. This study aimed to evaluate the pathogenicity of *BRCA2* VUS detected by next-generation sequencing (NGS) in patients at the Çanakkale Onsekiz Mart University Medical Genetics Clinic and explore their clinical relevance.

Methods:

VUS interpretations were performed using Franklin, ClinVar, and QCI databases. Functional effects were assessed using in silico tools including SIFT, MutationTester2021, FATHMM, PANTHER, and AlphaMissense. Disease associations were evaluated using PHD-SNP and SNPs&GO, while MUpro and I-Mutant assessed protein stability. HOPE and Swiss-Model were used for 3D structural analysis. Findings were correlated with patients' personal and family cancer histories.

Results:

Among 193 *BRCA2* variants, 53% were benign/likely benign, 21% pathogenic/likely pathogenic, and 24% VUS. The study focused on 48 VUS—all missense variants, mostly in exon 11. In silico analyses reclassified 7 as pathogenic/likely pathogenic and 29 as benign/likely benign. Conflicting results were observed for 12 variants. Additionally, 7 novel variants were identified.

Conclusıon:

In silico tools were effective in reassessing *BRCA2* VUS, reducing the VUS rate from 24% to 6%. These results support the integration of computational predictions into clinical genetics workflows. Further functional studies are needed to clarify the biological impact of unresolved variants and improve genetic counseling in hereditary cancer.

Keywords: *BRCA2*, VUS, in silico, clinic correlation

PP7- Evaluation of the hereditary cancer relationship of the fanconi anemia gene family

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Introduction: The Fanconi Anemia(FA) pathway is crucial for DNA repair and genomic stability. While biallelic mutations

in the FA pathway are linked to Fanconi anemia, the role of heterozygous mutations in certain FA genes in cancer development is still unclear. This study aims to assess the association of heterozygous pathogenic or likely pathogenic variants in FA gene family members, excluding cancer related *BRCA1,BRCA2,BRIP1,PALB2,RAD51C* and *RAD51* with hereditary cancer risk and their effects on DNA repair mechanisms.

Materials and Methods: In this retrospective study, patients who applied to our clinic and were found to have heterozygous pathogenic or likely pathogenic variants in the *FANCA,FANCB,FANCC,FANCD2,FANCE,FANCF,FANCG,FANCI,FANCM,SLX4,ERCC4,XRCC2,UBE2T,MAD2L2,RFWD3,FANCL* genes as a result of NGS analysis were examined.

Conclusions: Nineteen patients with variants in FA genes were analyzed. Four had a personal history of cancer, including breast cancer (2 cases), thyroid cancer, and a CNS tumor. Fourteen patients had family or personal histories of cancer, with breast cancer being most common, alongside lung, colon, stomach, pancreas, endometrium, prostate, bladder, larynx cancers, leukemia, Wilms tumor, and CNS tumors. Five patients had no personal or family history of cancer. It has been determined that the cancer risk is increased by 2.37 times in individuals carrying the mutation.

Discussion: This study adds to the literature by exploring the impact of heterozygous FA mutations on cancer susceptibility. The findings suggest that individuals with heterozygous variants in FA genes may be at an increased risk for various cancers, which may inform future strategies for cancer diagnosis, prevention, targeted therapies, and genetic counseling.

Keywords: cancer, DNA repair, Fanconi anemia

PP8- Renpenning Syndrome: Frameshift PQBP1 Variant in a Patient with Fragile X-Like Phenotype

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Background/Objectives: PQBP1 gene encodes the polyglutamine-binding protein 1 (PQBP1), which is involved in mRNA splicing and transcription. Pathogenic variants in this gene cause X-linked mental retardation disorders collectively referred to as Renpenning syndrome; characterized by microcephaly, short stature, small testes, and dysmorphic facial features. This report aims to present a case featuring intellectual disability along with dysmorphic characteristics, linked to a pathogenic mutation in the PQBP1 gene.

Methods: Following DNA isolation from peripheral blood; array-CGH analysis, CGG trinucleotide repeat analysis of the FMR1 gene and, whole exome sequencing (WES) analysis using the xGenExomeResearch Panel v2 kit via the NGS method were conducted.

Results: A 7-year-old male patient was referred to our clinic due to developmental and language delay with a preliminary diagnosis of Fragile X syndrome. The patient has speech delay, developmental delays, and learning difficulties, and unable to cooperate with the intelligence test. In a physical examination, microcephaly, long triangular face, sparse eyebrows, prominent eyelashes, thin upper lip, long philtrum, upslanted palpebral fissures, and proximally placed thumb were observed. Chromosome analysis and Fragile x, microarray, analyses were found to be normal. In WES analysis (NM_001032382.2) PQBP1 c.450_453delCAGA;p.D150fs*44 pathogenic frameshift deletion was detected.

Conclusion: Renpenning syndrome, due to its initial resemblance to Fragile X syndrome, requires considering Fragile X syndrome as a differential diagnosis. Clinical parameters such as head circumference, testicular volume, and height play a role in distinguishing between the two syndromes during first examination, thereby guiding further diagnostic tests and improving diagnostic accuracy.

PP9- Copy number variants in pediatric epilepsy patients

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Abstract

Introduction:

Epilepsy is one of the most common chronic neurological disorders of childhood, affecting over 10 million children globally. Identifying the underlying cause is essential for appropriate treatment planning and prognosis estimation. This study aimed to determine the frequency of copy number variants (CNVs), known to be associated with neurodevelopmental disorders such as intellectual disability, autism, epilepsy, and psychiatric conditions, in patients diagnosed with epilepsy within the first 18 years of life, and to characterize the clinical features of those carrying pathogenic CNVs.

Materials and Methods:

Medical records of patients referred to the Medical Genetics Clinic of our hospital with a diagnosis of epilepsy between 2013 and 2025 were retrospectively reviewed, provided informed consent was obtained. Patients who underwent microarray analysis using the Illumina CytoSNP-12v2.1 BeadChip (315K) platform on DNA extracted from peripheral blood and were found to have CNVs were included.

Results:

Among 168 pediatric epilepsy patients, at least one CNV was

detected in 13 (7.7%). Of these, 7 (53.8%) were male and 6 (46.2%) female. The mean age was 6.77 years; the median was 6.39 years. CNVs included 7 duplications (53.8%) and 6 deletions (46.2%). The most commonly affected region was 16p11.2 (30.8%), linked to neurodevelopmental disorders. Deletions ranged from 660 kb to 1.1 Mb. CNVs involving sex chromosomes were observed in two patients, consistent with karyotype analysis. Three variants were of uncertain significance; nine were pathogenic. No reclassification occurred upon database review.

Conclusion:

CNVs are significant contributors to pediatric epilepsy. Microarray analysis offers valuable diagnostic insight, especially in early-onset, unexplained cases.

Keywords: Copy number variants, microarray analysis, pediatric epilepsy

PP10- Link between chronic tinnitus with *mir-30e*, *mir-206,* and *mir-124* polymorphisms modulating the brain-derived neurotrophic factor gene

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Introduction

Brain-derived neurotrophic factor (BDNF) is involved in early development of the central auditory pathway and inner ear sensory epithelium. Mounting evidence indicates that BDNF administration promotes miRNA production in neurons, despite the typical suppressive effect of miRNAs on *BDNF* expression. Therefore, miRNAs regulating *BDNF* expression may have an impact on the auditory pathway and could be potential gene polymorphisms affecting human hearing ability. This study aimed to examine the role of miRNA polymorphisms regulating *BDNF* in the pathophysiology of tinnitus.

Materials and Methods

The study recruited 70 tinnitus patients aged 18-55 from the ENT clinic, along with 70 control subjects of the same age range without tinnitus or systemic illnesses. Tinnitus assessment included tympanometric, audiological, and psychoacoustic evaluations. Seven *miRNA* SNPs (*miR-30e rs112439044, rs10489167, miR-206 rs16882131, miR-30a rs1491500379, miR-26b rs565919718, rs188612260,* and *miR-124 rs5315564*) regulating the *BDNF* gene were analyzed using the Fluidigm platform.

Results

Significant differences in genotype distribution were observed for *miR-30e rs112439044*, *miR-124 rs5315564*, and *miR-206 rs16882131* polymorphisms between the tinnitus and control groups ($p<0.05$). According to genetic inheritance-model analysis, the dominant and additive inheritance models revealed 0.20 and 0.83-fold risks for *miR-30e rs112439044*, respectively. The dominant inheritance model showed a 1.65-fold risk for *miR-124 rs5315564*, while the dominant model had an 11.1-fold protective effect for *miR-206 rs16882131* and the additive model had an 8.57-fold risk.

Discussion and Conclusions

The study results indicate that *miR-206*, *miR-30e*, and *miR-124* polymorphisms may influence the auditory pathway through the regulation of *BDNF* gene expression.

Keywords: Chronic tinnitus; *BDNF* gene; *BDNF* gene regulating *miRNAs;* Single nucleotide polymorphism

PP11- A rare syndromic immunodeficiency caused by *ZBTB24* gene

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Introduction: Immunodeficiency-Centromeric Instability-Facial Anomalies Syndrome (ICF syndrome) is a rare genetic disorder characterized by humoral immunodeficiency, dysmorphic facial features, and marked genomic instability, notably in the centromeric regions of chromosomes 1, 9, and 16. The syndrome is inherited in an autosomal recessive manner and four genes have been identified associated with the relevant phenotype: DNMT3B, ZBTB24, CDCA7, HELLS. Here, we present a case with ICF syndrome caused by a homozygous nonsense ZBTB24 variant.

Case Report: 7-year-old male patient was referred from the department of allergy and immunology for a definitive molecular diagnosis. He first presented at the age of 8 months with recurrent fever and bronchiolitis. Further evaluation was significant for hypogammaglobulinemia and dysmorphic facial features, including flat and wide nose bridge, hypertelorism, upslanting palpebral fissures, and a bilateral sandal gap deformity. Based on these findings, the patient was clinically diagnosed with ICF syndrome and scheduled for regular follow-up with IVIG injections. He also has speech delay and specific learning disorder. To clarify underlying pathology, karyotyping was initially performed, which demonstrated chromosomal instability. Subsequently, he underwent Clinical Exome Sequencing (QIA-

seq-Actionable Exome Kit), in which homozygous p.R320* variant was identified in the ZBTB24 gene.
Conclusion: This case highlights the importance of considering ICF syndrome in patients presenting with immunodeficiency and facial dysmorphism. Karyotyping that reveals genomic instability remains a valuable method where molecular tests are not available in patients with suspected ICF syndrome.
keywords: syndromic, immunodeficiency, ZBTB24, ICF

PP12- A Novel homozygous *CUL7* variant in a patient with 3M syndrome: Clinical presentation and molecular diagnosis

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Abstract:
Background: 3M syndrome is a rare autosomal recessive disorder characterized by severe pre- and postnatal growth retardation, characteristic facial dysmorphism, skeletal anomalies, and normal intelligence. Pathogenic variants in *CUL7*, *OBSL1*, and *CCDC8* genes are known causes.
Case Presentation: We report a 2-year and 3-month-old female patient referred from pediatric endocrinology due to marked short stature and coarse facial features. She was born at 33 weeks of gestation to consanguineous parents (G2P2A0), weighing 1350 grams, and required 2.5 months of neonatal intensive care for respiratory distress syndrome. Psychomotor development was normal. Newborn screening, hearing, and vision tests were unremarkable. Family history revealed short stature in the father's aunt and uncle. On physical examination, height was 71 cm (<0.02 percentile), weight 8.9 kg (0.25 percentile), and head circumference 48 cm (43.25 percentile). Dysmorphic features included dolichocephaly, coarse facial appearance, thick eyebrows, synophrys, depressed nasal bridge, broad nasal tip, anteverted nostrils, long philtrum, high narrow palate, and a simian crease on the left hand. Abdominal ultrasound, skeletal survey, echocardiography (closed VSD), and metabolic screening were normal.
Results: Clinical exome sequencing identified a novel homozygous frameshift variant in *CUL7* (NM_014780.5:c.317del, p.Val106Glyfs*9), classified as likely pathogenic (PM2, PVS1) according to ACMG criteria.
Conclusion: A comprehensive phenotypic evaluation is crucial in patients with growth retardation to identify underlying genetic causes. 3M syndrome should be considered in individuals with characteristic craniofacial and skeletal features. The novel *CUL7* variant identified in our patient adds to the mutational spectrum of this rare syndrome and highlights the importance of molecular genetic analysis in diagnosis.
Keywords: 3M syndrome, *CUL7* gene, short stature

PP13- Clinical and genetic evaluation of 16 patients diagnosed with Prader-Willi Syndrome

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Introduction: Prader-Willi syndrome (PWS; OMIM #176270) is a rare genetic disorder characterized by hypotonia, intellectual disability, short stature, hypogonadotropic hypogonadism, and a distinct nutritional trajectory-initial feeding difficulties followed by hyperphagia and obesity. It results from abnormal DNA methylation in the 15q11.2–q13 region, most commonly due to paternal deletions, followed by maternal uniparental disomy and imprinting defects.
Materials and Methods: We retrospectively evaluated the demographic and clinical characteristics of 16 patients diagnosed with PWS and followed at our clinic between 2014 and 2025. Data were analyzed using SPSS version 20.
Results: Eight of the patients were female (50%). The median age at diagnosis was 5 months and 10 days, and 12 patients (85.7%) were diagnosed during infancy. IUGR was present in 8 patients (50%), and 15 (93.7%) required NICU admission. All had neonatal hypotonia; 13 (81%) had feeding difficulties, and 10 (62.5%) experienced respiratory distress. At last follow-up, five patients were still in infancy, with a median weight SDS of -1.86 (range: -2.84 to -0.78) and head circumference SDS of -2.49 (range: -3.16 to -1.45). Among the 10 patients aged 2 years and older at the last follow-up, 7 were found to be obese (BMI > +2 SDS). Genetic analysis revealed deletions in 64% of patients and uniparental disomy in the remainder; no imprinting center defects were detected.
Conclusion: PWS should be considered in neonates presenting with IUGR, hypotonia, feeding difficulties and respiratory distress. Early diagnosis is critical to address nutritional management and prevent neuromotor delays.
Keywords: Prader-Willi Syndrome, genetics, nutrution, obesity.

PP14- A Novel Splice-site Variant in A 17-year-old Male Patient with Basilicata-Akhtar Syndrome

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Introduction: Basilicata-Akhtar Syndrome (MRXSBA) is characterized by global developmental delay, feeding difficulties, hypotonia, poor or absent speech, unsteady gait and spasticity. Additional findings include dysmorphic facial features and mild distal skeletal anomalies. MRXSBA is caused by variations in *MSL3*. We present a 17-year-old male patient who has been diagnosed by clinical exome sequencing (CES).

Material, Methods: A 17-year-old male patient was consulted to our clinic for mental retardation, neurodevelopmental delay, joint contractures, and sensorineural hearing loss. The patient had a history of achilles tendon contracture and cryptorchidism surgeries. It was known that the mother had intellectual disability. In our physical examination, brachycephaly, pectus carinatum, joint stiffness and increased muscle tones were observed. The facial dysmorphic features included Widows's peak, left epichantal fold, long and narrow chin, posterior rotated prominent ears, and dental anomalies. Cranial MRI findings were as follows; cerebral and cerebellar atrophy, thin pituitary gland, and gliotic changes in the periventricular and subcortical white matter.

Discussion: To elucidate underlying pathology, chromosomal microarray analysis and karyotyping were performed, both of which resulted normal. Subsequent clinical exome sequencing revealed a hemizygous splice variant in *MSL3* gene (NM_078629.4:c.1282-1G>A). This variant was interpreted as likely pathogenic according to ACMG 2015 variant classification and considered to be associated with patient's phenotype.

Conclusion: Thus far, over 40 patients with Basilicata-Akhtar Syndrome have been documented, and all reported variants were *de novo*. In our case, due to the presence of intellectual disability in the mother, a family study is being conducted to investigate a possible hereditary transmission. A novel splice-site variant was identified at the acceptor side of exon 11, within the region encoding the critical MRG domain.

KeyWords: Basilicata-Akhtar Syndrome, MSL3, splice variant

PP15- Identification of a novel pathogenic *EXT1* gene mutation in a patient with multiple osteochondromas

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Backround

Multiple Hereditary Osteochondromas(MHO) previously known as Multiple Hereditary Exostoses(MHE) is characterized by growth of multiple osteochomdromas. These are benign bone growths that typically form at the ends of long bones, particularly in the metaphyseal areas, and grow outward covered by cartilage. We report a patient with a novel pathogenic *EXT1* gene mutation inherited paternally, who presented with multiple osteochondromas.

Material and Methods

Genomic DNA materials were isolated from the peripheral blood samples of the family members which were obtained after informed consent was taken. Conventional karyotyping and whole-exome sequencing (WES) were performed concurrently. To confirm the findings and perform segregation analysis, Sanger sequencing was utilized.

Results

A 4-year and 2-month-old male child, born to unrelated parents, was referred to our clinic due to the presence of multiple painless palpable bone masses, which were first noticed by the parents six months earlier. The lesions progressively grew in number and size. Axial radiography revealed multiple osteochondromas on the long bones. Conventional karyotyping revealed a normal 46,XY karyotype. WES identified a novel paternally inherited mutation in the *EXT1* gene [c.640_659del]. The father of the patient also exhibited multiple exostoses, along with a limb length discrepancy.

Conclusion

We report a novel pathogenic *EXT1* mutation that causes multiple hereditary exostoses in both our patient and his father. This mutation is expected to cause a frameshift in the ribosome reading frame leading to premature termination of the *EXT1* protein.

PP16- Williams syndrome: Phenotypic features of 10 Turkish patients

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Introduction:

Williams Syndrome (WS, OMIM194050) is a multisystemic genetic disorder characterized by developmental delay, intellectual disability, distinctive facial features, cardiovascular disease and renal, endocrinological, ocular, auditory, connective tissue anomalies. It is usually caused by a de novo microdeletion in the Williams-Beuren Syndrome Critical Region at 7q11.23, which includes *ELN, CLIP2, GTF2I, GTF2IRD1, LIMK1* genes. In this study, we examined the phenotypic features of 10 patients presenting with dysmorphic facial features and developmental delays.

Materials and Methods:

Ten patients, who were followed in our outpatient clinic with a diagnosis of Williams Syndrome, were included in the study. Phenotypic features were obtained from patient records retrospectively.

Results:
Patients median ages of the patients was 37.5 months (70 days and 12 years). Two patients were male, eight were female. All patients exhibited common dysmorphic features including broad forehead, periorbital fullness, long philtrum, thick lips, wide mouth and developmental delay. Nine patients had cardiovascular disease, three had hypothyroidism, two had nephrolithiasis and one had hypercalcemia. The most common cardiac anomalies were supravalvular aortic stenosis (4/9), mitral valve insufficiency (4/9). Diagnosis was confirmed in all patients by fluorescence in situ hybridization.
Conclusion:
Morbidity and mortality are increased 25- to 100-fold due to complications. Awareness of the typical facial features is crucial for early diagnosis and treatment. Microarray analysis can define the extent of deletions. Deletion of the *ELN* gene is responsible for arteriopathy and connective tissue abnormalities. Further studies are needed to elucidate the clinical outcomes of the deletions.
Keywords: Williams syndrome, 7q11.23, ELN

PP17- The role of high-resolution testing in rare disease diagnosis: case presentation
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Introduction
Advancements in technology have significantly improved the ability to diagnose rare diseases. Genetic tests are usually performed once in a lifetime. However, with an increased resolution test, it is advisable to take the test again.
Case presentation
We report a case of an 8-year-old girl with hydrocephalus and dysmorphic features, including hypertelorism, ptosis, downturned palpebral fissures, brachydactyly, clinodactyly, high-arched palate, and caudal appendage. She was referred due to developmental delays, including delayed walking (at 4 years) and speech development. Additionally, a hearing test revealed left-sided hearing loss. Her parents are first cousins, and her family history was unremarkable. Growth parameters were notably below average, with a height of 111 cm (SDS: -3.49). Cardiac evaluation showed ASD and PDA, and abdominal ultrasound revealed horseshoe kidneys.
Result
Genetic testing (Array CGH 8x60K ISCA) revealed a 4.2 MB interstitial deletion at 4p16.3 in 2017. In addition to the previous array analysis, higher-resolution microarray (SNP 6.0 Cytogenetics (Affymetrix) testing identified a 16 kilobase homozygous deletion in the *MASP1* gene (exons 1 and 2). CES (Clinical Exome Sequencing) in which Copy Number Variation (CNV) analyses were integrated also confirmed this homozygous deletion.
Discussion
This case highlights the utility of advanced genetic technologies, such as microarray and CNV analysis, in detecting small genomic changes that were previously undetectable, offering a more accurate diagnosis of rare genetic disorders and potential for targeted interventions. If a genetic alteration found does not deeply explain the patient's clinical findings, the patient should be reevaluated for higher-resolution test.
Keyword: High-resolution testing, Dysmorphic feature, *MASP1* gene deletion

PP18- Investigation of molecular prevalence and molecular characterization of zoonotic Cryptosporidium species in human and animal hosts
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Abstract
Introduction: Cryptosporidiosis is an infectious disease caused by Cryptosporidium species. In general, it was aimed to reveal the prevalence and genotypic diversity of the parasite against cyriptosporodiosis caused by Criptosporidium species by investigating the transmission between animal and human hosts at the molecular level. Therefore, the project titled "Investigation of Molecular Prevalence and Molecular Characterization of Zoonotic Criptosporidium Species in Human and Animal Hosts" was designed.
Materials and Methods: For this purpose, PCR and QPCR tests were performed after DNA isolation of stool samples collected from human and animal hosts and the samples detected to be positive for Criptosporidium species were purified and sent to the company from which the service was purchased for sequence analysis. The obtained sequence information was analyzed using phylogenetic tools.
Discussion: As a result of the phylogenetic examination of the samples detected positive in cat, dog and calf samples together with their breeders, it was determined that animal isolates and human isolates - within each group - had similar sequences and phylogenetic characters. It was found to be similar. The study is unique in that it is the first study to show the molecular level of transmission among dog, cat, horse, cattle and poultry groups and among those who raise them.
Results: Therefore, it is thought that examining the symptoms and elucidating the relationship between symptoms and parasite genotypes will contribute to diagnostic studies as well as epidemiological studies. The data obtained will form the basis

of various studies to be conducted in the future.

Keywords: Cryptosporidium, Zoonosis, Molecular characterization, PCR

PP19- Molecular prevalence and molecular characterızatıon of dıentamoeba fragılıs ın patıents dıagnosıs of cancer

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Abstract

Introduction: Dientamoebiasis is an infection caused by Dientamoeba fragilis. Data on the relationship between the molecular types of this parasitosis, which is of increasing importance especially in cancer patients, and cancer diseases are limited. This study aimed to obtain new data on the relationship between its molecular characteristics and the disease.

Materials and Methods: The study included stool samples collected from patients and healthy volunteers who would form the control group. In the study, PCR and qPCR tests were performed after total genomic DNA isolation of the collected samples, and phylogenetic characterization was performed by obtaining sequence analysis of the samples found to be positive for *Dientamoeba fragilis*.

Discussion: Accordingly, 6 patient was detected as positive with standard PCR, while 11 patient was detected as positive with qPCR. It was shown that there was no significant difference in the distribution of the parasite between male and female patients diagnosed with cancer. The different genotype was detected in cases infected with *D. fragilis*.

Results: In conclusion, this study has shown that there may be a molecular relationship between patients diagnosed with cancer and the genotypes detected in this parasite, which is thought to affect clinical findings. It is a study that sheds light on the effect of the genotypes of the parasite on clinical symptoms in the cases included in the study. It is thought that this study will contribute to diagnostic studies as well as epidemiological studies.

Keywords: *Dientamoeba fragilis*, Cancer, Genotyping

PP20- Expanding the Genotypic Spectrum of DNM1L-Associated EMPF1: A Case Report of a Novel Variant

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Abstract

DNM1L encodes dynamin-related protein 1 (DRP1), a large GTPase essential for mitochondrial and peroxisomal fission. Heterozygous, mostly de novo pathogenic variants in *DNM1L* cause Encephalopathy, lethal, due to defective mitochondrial and peroxisomal fission 1 (EMPF1), an autosomal dominant disorder characterized by developmental delay, refractory seizures, neurologic regression, and cerebral atrophy.

We present the case of an 11-year-old girl referred to our clinic with refractory status epilepticus lasting 15 hours. Seizures began with numbness in the left arm and progressed to generalized tonic-clonic convulsions. At admission, she was unconscious, intubated, and receiving multiple antiepileptic medications. Her medical history included bilateral ptosis since the age of five, attention deficit, learning difficulties, and episodes of aggressive behavior. No dysmorphic features or parental consanguinity were noted. Brain imaging revealed cerebral atrophy. Initial differential diagnoses included infectious or autoimmune encephalitis, mitochondrial disorders, and GLUT1 deficiency.

Whole exome sequencing revealed a novel heterozygous in-frame deletion in exon 14 of the *DNM1L* gene. We classified the variant as likely pathogenic according to the ACMG criteria. The clinical presentation was consistent with previously reported cases of *DNM1L*-related encephalopathy. No biochemical abnormalities indicating mitochondrial or peroxisomal dysfunction were detected, underscoring the diagnostic value of genomic analysis. This variant has not been previously reported in the literature and was confirmed as de novo.

Keywords: *DNM1L*, mitochondrial fission, in-frame deletion, status epilepticus, cerebral atrophy.

PP21- Clinical and laboratory comparison of patients with compound heterozygous MEFV P369S-R408Q variants and M694V mutations

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Introduction:

Familial Mediterranean Fever (FMF) is the most common hereditary autoinflammatory disorder, characterized by recurrent febrile attacks and serosal inflammation. While MEFV:p.P369S and p.R408Q variants are classified as variants of uncertain significance (VUS), recent studies suggest that their compound heterozygosity may be associated with autoinflammatory phenotypes. This study compares the clinical and laboratory features of patients carrying compound heterozygous

P369S-R408Q with those carrying M694V mutations.
Methods:
We retrospectively evaluated 86 patients with MEFV mutations and complete clinical/laboratory data. Genetic analyses were performed at Çanakkale Onsekiz Mart University. Patients were grouped as follows: Group A (n=28) – compound heterozygous P369S-R408Q; Group B (n=43) – heterozygous or compound heterozygous M694V; Group C (n=15) – homozygous M694V.
Results:
Group C exhibited higher levels of serum amyloid A, CRP, and ESR compared to Groups A and B, indicating a more pronounced inflammatory response. Group C also fulfilled the Tel-Hashomer criteria more frequently. While overall inflammation markers were comparable between Groups A and B, clinical features such as pleuritis and erysipelas-like erythema were less common in Group A. Colchicine treatment response was observed in all groups, with no significant differences.
Conclusion:
Although P369S and R408Q are VUS, their compound heterozygosity may be associated with FMF-like symptoms. Despite the milder clinical course and lower frequency of key diagnostic findings, colchicine therapy appears effective. FMF should be considered in such patients, and colchicine should be initiated when clinically indicated.
Keywords: FMF, M694V, P369S, R408Q

PP22- 22q11.2 Deletion Syndrome Presenting with Multisystemic Findings: A Case Report of a 19-Year-Old Male
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Introduction:
22q11.2 deletion syndrome (DiGeorge syndrome) is a genetic disorder caused by a microdeletion in the 22q11.2 region, characterized by multisystem involvement. Developmental delay, immunodeficiency, congenital heart defects, palatal anomalies, and neuropsychiatric manifestations are among the most frequently observed features.
Case Presentation:
We present a 19-year-old male with a history of cerebral palsy, epilepsy, diabetes mellitus, and recurrent pneumonia. Hypotonia was identified during infancy, generalized tonic-clonic seizures began at the age of six, and diabetes mellitus was diagnosed one year ago. The patient also had a history of deep vein thrombosis secondary to immobilization following pneumonia. Cranial imaging revealed polymicrogyria and calcifications. Array comparative genomic hybridization (aCGH) analysis identified an approximately 2.5 Mb heterozygous deletion in the 22q11.2 region (chr22:18,893,637–21,415,067), including critical genes such as *TBX1* and *CRKL*, and this finding was confirmed by FISH analysis.
Discussion:
This case demonstrates the broad phenotypic spectrum of 22q11.2 deletion syndrome, involving neurological, endocrine, and immune systems. Interestingly, the absence of cardiac findings in our patient indicates an atypical presentation of the syndrome. Early implementation of molecular and cytogenetic analyses is crucial for accurate diagnosis and appropriate clinical management.
Conclusion:
This case highlights the importance of early genetic testing in patients with multisystemic manifestations and clinical suspicion of 22q11.2 deletion syndrome. Timely diagnosis enables appropriate treatment planning and facilitates effective genetic counseling for affected families.
Keywords: 22q11.2 deletion syndrome, cerebral palsy, epilepsy, genetic counseling

PP23- A Novel KRT6A Variant in Pachyonychia Congenita
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Introduction:
Pachyonychia congenita (PC) (OMIM #615726) is a rare genodermatosis characterised by hypertrophic nail dystrophy, painful palmoplantar keratoderma, oral leukokeratosis, pachyonychia, pilosebaceous cysts, palmoplantar hyperhidrosis, and follicular keratosis on the trunk and extremities. It is inherited in an autosomal dominant pattern, and approximately 30% of cases arise *de novo*. PC is caused by mutations in keratin genes (*KRT6A, KRT6B, KRT16, KRT17*). The *KRT6A* gene, associated with PC type 3, is located on chromosome 12q13.13 and encodes keratin 6A, a type II cytokeratin essential for maintaining epithelial structural integrity.
Case Report:
A 20-year-old male was referred by dermatology for palmoplantar keratoderma manifested at birth. Palmoplantar keratoderma, painful plantar keratosis, oral leukokeratosis, onychogryphosis of the toenails and pachyonychia of the fingernails were observed on physical examination. There was no parental consanguinity, but similar findings were observed in four siblings, the father, grandfather, uncle, and the uncle's four children. A genetic panel for suspected PC identified a heterozygous c.1384A>T (p.Ile462Phe) variant in *KRT6A*.
According to ACMG guidelines, this variant was classified as likely pathogenic. Segregation analysis was planned for the patient's parennjujts and siblings.
Conclusion:
This case presentation highlights a previously unreported *KRT6A* variant associated with PC, expanding the known mutational spectrum of the disease. Recognition of clinical features

alongside genetic confirmation is essential for accurate diagnosis and appropriate management. Furthermore, identifying pathogenic variants allows for effective genetic counselling and family screening in inherited genodermatoses.

Keywords: Pachyonychia congenita, *KRT6A*, keratin

PP24- Robinow syndrome in a family: Two cases with variable penetrance

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Introduction: Robinow syndrome is a rare genetic disorder that affects the development of the skeletal system and various structures of the body. In Robinow syndrome, shortening of the long bones in the arms and legs, braidactyly, vertebral anomaly, short stature, fetal face and ambiguous genitalia are common symptoms. The autosomal recessive Robinow syndrome with more severe clinical course has been described in less than 200 individuals in the literature. The autosomal dominant form has been diagnosed in approximately 50 families.

Materials and Methods: An infant aged 7 months male patient was referred to us from the pediatric endocrinology outpatient clinic with a prediagnosis of sexuel development disorder. Detailed anamnesis revealed micropenis and fetal face. The patient underwent conventional cytogenetic analysis and sexual development disorder panel by NGS method.

Conclusion: Conventional cytogenetic analysis showed a normal 46,XY karyotype with no sex chromosome abnormalities. DNA sequencing identified a heterozygous pathogenic variant in the DVL1 gene, associated with autosomal dominant Robinow syndrome. Segregation analysis confirmed the variant in the heterozygous state in the father.

Discussion: Robinow syndrome is a rare genetic disorder that occurs in approximately 1/1,500,000 live births worldwide. This case was diagnosed as Robinow syndrome with an autosomal dominant inheritance pattern. Since complete penetrance is not observed in this inheritance pattern, the variant observed in the index patient was also detected in the father, but no clinical findings were observed in the father.

Keywords: *DVL1* gene, *Robinow Syndrome, Next-generation sequencing (NGS)*

PP25- The role of type 3 immunity in Pediatric Cystic Fibrosis

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Abstract

Background: Cystic Fibrosis (CF) is an autosomal recessive disease affecting the respiratory tract, pancreas, intestine, exocrine, male genital system, hepatobiliary system and exocrine sweat glands due to dysfunction of exocrine glands as a result of mutations in the Cystic Fibrosis Transmembrane Regulator (CFTR) gene. The defective CFTR gene causes protein degradation, leading to dehydration of the airway surface and thick mucus accumulation. Although the levels of IL-17A, IL-23, IL-22 cytokines have been shown to increase in CF, the relationship between type 3 immunity and CF is still controversial.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from blood samples of control (n = 20), patient (n = 20) and attack groups (n = 8) by creating a density gradient with Ficoll-Hypaque and serum was collected. In order to determine the amounts of intracellular cytokines, cells were stimulated with PMA-ionomycin and Golgi stop. Cytokine staining was performed for IL-17, IL-22, IL-10 using Cytofix/Cytoperm™ kit. ELISA was performed for IL-17A, IL-22 and GM-CSF from the serum.

Results: When the percentages and absolute numbers of CD3+IL-17+ and CD3-IL-17- cells were compared between the groups, no statistically significant difference was found. However, the absolute number and percentage of CD3+IL-22+ cells had a significant difference between the groups. In addition to these results, increased IL-17A levels were shown in plasma by ELISA.

Conclusions: These results indicate that Th17-related cytokines have significant effects in CF patients and affect the prognosis of the disease.

Keywords: Cystic Fibrosis, IL-10, IL-17, IL-22, GM-CSF

PP26- SYNE1 Gene De-Novo Variant In Autosomal Recessive Spinocerebellar Ataxia Type 8

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Introduction: Cases presenting with a clinical prediagnosis of SCA are diagnosed with molecular genetic tests.The estimated worldwide prevalence of SCAR8 disease due to SYNE1 variants is less than 1 million.

Materials and Methods: In this study, we report a 29-year-old woman who presented with stiff neck, tinnitus, weakness in arms and inability to walk unassisted. Neurological examination of the patient revealed significant cerebral findings and MRI performed at an external center revealed brain shrinkage. After detailed anamnesis of the patient, pedigree was obtained.
Discussion: While the parents had a complaint of staggering, the older sister had staggering since she was young but did not need any help. Similar indications were also found in previous generations. The patient was included in the ataxia panel using the NGS method. The SYNE1 gene was found to be a de novo frameshift variant. In line with the molecular genetic results for this patient, their parents and a sibling with similar clinical findings were invited to our department for screening for the variant detected in the SYNE1 gene.
Results: The patient's clinical and genetic diagnosis was consistent with autosomal recessive spinocerebellar ataxia type 8. In addition to the autosomal recessive inheritance of the highly pathogenic variant in the SYNE1 gene, the patient's homozygosity indicates that we made a molecular genetic diagnosis that supports the clinical findings. In conclusion, our aim in presenting this case was to contribute to the literature by adding a de novo variant.
Keywords: Ataxia, SCA type 8, SYNE1/SCAR8, prevalence

PP27- A late-diagnosed case of cornelia de lange syndrome with a BRD4 variant
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Introduction:
Cornelia de Lange syndrome (CdLS) is a genetically heterogeneous condition with distinctive facial features, growth delay, intellectual disability, and multiple congenital anomalies. Variants in **NIPBL** are most common, followed by **HDAC8** and **SMC1A**, with less frequent involvement of **RAD21**, **SMC3**, and **BRD4**. Since the CdLS phenotype may evolve, diagnosis can be delayed—especially in adolescents. Early childhood features can therefore aid recognition. This report presents a late-diagnosed CdLS case with a **BRD4** variant.
Case Presentation:
A 17-year-old male was referred to the genetics clinic for choanal atresia, short stature, and borderline intellectual disability. He was born at 36 weeks by cesarean section with a birth weight of 1500 grams and required neonatal intensive care due to cyanosis and absent crying. He had been followed by endocrinology for short stature (–3.81 SDS). Physical exam showed microcephaly, scoliosis, unilateral gynecomastia, and clinodactyly. Karyotype was normal. Due to the combination of clinical findings, a broad next-generation sequencing panel was planned. It identified a heterozygous missense variant in the **BRD4** gene (c.1289A>G, p.Tyr430Cys), classified as likely pathogenic.
Conclusion:
CdLS was not initially suspected due to a non-classic facial appearance. However, multiple clinical features prompted comprehensive genetic testing, which confirmed the diagnosis. Later review of childhood photographs revealed facial traits consistent with CdLS. This case illustrates how evolving phenotypes can complicate recognition and underscores the value of broad molecular testing. Reporting BRD4-related cases also contributes to expanding the CdLS genetic spectrum.
Keywords: Cornelia de lange syndrome, CdLS, BRD4, NGS

PP28- Freeman-Sheldon Sendromlu Olguda Prenatal Genetik Danışmanlık Önemi
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Giriş: Freeman-Sheldon sendromu (FSS), distal artrogripozis tip 2A (DA2A) olarak da bilinen, *embryonic myosin, heavy chain 3, skeletal muscle* (*MYH3*, OMIM no * 160720) genindeki patojenik varyantlara bağlı nadir, otozomal dominant geçişli konjenital bir kontraktür bozukluğudur. Burada otozomal dominant kalıtımlı nadir hastalıklara sahip bireylerde prenatal genetik tanı ve genetik danışmanlığın öneminden bahsedilecektir.
Yöntem: Prenatal ultrasonografide artmış nazal kemik kalınlığı, iskelet anomalileri saptanan 29 yaşındaki gebe hasta değerlendirildi. Hastanın yapılan ayrıntılı dismorfik muayenesinde kısa boy, kısa boyun, uzun filtrum, küçük ağız, H-şeklinde çene çukuru, pitoz, strabismus, kamptodaktili, ve kifoskolyos yer almaktaydı. Hastaya tüm ekzom sekanslama yapıldı.
Bulgular: Hastada, yeni nesil dizileme ile *MYH3* geninde c.533C>T (p.Thr178Ile) heterozigot varyantı tanımlandı. Bu mutasyon, Freeman-Sheldon sendromu ile ilişkilidir.
Tartışma: Otozomal dominant kalıtım nedeniyle, her gebelikte %50 geçiş riski bulunmaktadır. Prenatal görüntülemede şüpheli bulgular (örneğin, artmış nazal kemik kalınlığı, ekstremite kontraktürleri) saptandığında hastanın gebelik haftası ile uyumlu olarak prenatal invaziv test önerilebilir. Bu vaka, özellikle aile temelli mutasyon taramasının dominant geçişli hastalıklardaki rolü, prenatal ultrason bulgularının tanı koymada yol göstericiliği, genotip-fenotip korelasyonunun kişiye özgü yönetim planlamasındaki katkısı gibi yönlerden önem

taşımaktadır. Ayrıca ebeveyn genotipinin bilinmesi, prenatal danışmanlık ve fetal risk değerlendirmesi açısından kritik önemdedir. Tıbbi Genetik ve Perinatoloji gibi disiplinlerin iş birliği, prenatal ve postnatal dönemde komplikasyonları önlemek açısından büyük önem taşır.

Anahtar Kelimeler: Freeman-Sheldon sendromu, MYH3, p.Thr178Ile, distal artrogripozis, prenatal tanı, konjenital kontraktür, genetik danışmanlık

PP29- Clinical And Molecular Evaluation of *ASXL3* and *KCNK4* Gene Variants in A Patient With Drug-Resistant Epilepsy, Psychomotor Regression, and Dysmorphic Features

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Introduction: Next-generation sequencing often reveals variants in complex cases. We report a 15-year-old female with drug-resistant epilepsy, psychomotor regression, fluctuating neutrophils, and white matter abnormalities. Genetic evaluation identified *ASXL3* and *KCNK4* variants, linked to Bainbridge-Ropers (BRPS) and FHEIG Syndromes. This report details her phenotype, evaluates these variants, and highlights diagnostic challenges.

Case Presentation: A 15-year-old female, born to consanguineous parents, experienced early-onset drug-resistant epilepsy and severe psychomotor regression after an 8-year-old seizure. She presents with microcephaly, balance disorder, involuntary movements, and dysmorphic features (e.g., facial asymmetry, long thumbs, prominent ears).

Findings: Profound developmental delay, severe microcephaly, and growth retardation were observed. Brain MRI showed non-specific FLAIR hyperintense lesions. WES revealed heterozygous *ASXL3* c.4966C>T p.His1656Tyr and KCNK4 c.660C>T p.Ala220= variants. Her complex phenotype overlaps significantly with core features of both BRPS (*ASXL3*-related) and FHEIG syndrome (*KCNK4*-related), including epilepsy and intellectual disability.

Discussion: Two distinct gene variants linked to severe, overlapping neurodevelopmental disorders suggest complex etiology. *ASXL3* missense variants, though atypical for truncating BRPS, can cause milder phenotypes. *KCNK4* splice region/synonymous variants may disrupt splicing, affecting neuronal excitability and contributing to epilepsy/developmental delay. While no direct digenic inheritance is established for *ASXL3*/*KCNK4*, their combined impact may explain her severe presentation. *HAX1*'s role in neutrophil/neurology adds complexity.

Conclusion: This case underscores diagnostic complexities in severe neurodevelopmental disorders with multiple genetic findings. Her extensive phenotype aligns with key BRPS and FHEIG features. Functional and parental segregation studies are crucial to elucidate precise pathogenicity and combined effects. This case expands the *ASXL3/KCNK4* phenotypic spectrum, emphasizing comprehensive molecular evaluation.

Keywords: *ASXL3, KCNK4*, epilepsy, psychomotor regression, dysmorphic features

PP30- FISH Yöntemi ile Belirlenen FIP1L1-PDGFRA Gen Rearranjmanlarının Retrospektif Olarak Değerlendirilmesi

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Abstract

Hypereosinophilic syndrome (HES) is a rare hematologic disorder characterized by persistent eosinophilia, tissue infiltration, and multi-organ involvement. Genetic abnormalities such as FIP1L1-PDGFRA, PDGFRB, FGFR1, and PCM1-JAK2 are known to play a crucial role in the pathogenesis, especially in myeloproliferative variants. This retrospective study analyzed the genetic and hematological data of 175 patients (87 females, 88 males) diagnosed with HES at Erciyes University between 2017 and 2023. FISH and karyotype analyses were used to identify gene rearrangements including FIP1L1-PDGFRA, t(5;12)(PDGFRB), t(8;13)(FGFR1), and t(9;12)(PCM1-JAK2). Additionally, demographic variables, eosinophil levels, and complete blood count results were evaluated. The findings indicated significantly elevated eosinophil counts in FIP1L1-PDGFRA positive patients and revealed meaningful correlations between mutation types and clinical parameters. This study emphasizes the importance of cytogenetic and molecular analysis in the accurate classification and targeted treatment of HES.

PP31- Exon 7 Matters: A Novel Frameshift Mutation in TALDO1 Expands the Phenotypic Spectrum of Transaldolase Deficiency

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Background:

Transaldolase deficiency is a rare autosomal recessive disorder caused by biallelic pathogenic variants in the TALDO1 gene. It disrupts the non-oxidative branch of the pentose phosphate pathway and manifests as a multisystemic condition involving liver, hematologic, renal, and connective tissues.

Case Description:

We present a 7-year-old girl with consanguineous parents,

evaluated for hepatosplenomegaly, biliary cirrhosis, nephrolithiasis, platelet dysfunction, secundum ASD, and mild skeletal anomalies. Remarkably, the patient exhibited a transient neonatal cutis laxa–like phenotype, a feature not previously reported in TALDO1 deficiency.

Whole-exome sequencing identified a novel homozygous frameshift variant in exon 7 of the TALDO1 gene: c.938del (p.Arg313ProfsTer8), predicted to result in loss of function. This variant is absent from population databases and not previously reported in ClinVar or HGMD. According to the 2020 ClinGen guidelines, the variant was classified as a VUS with PVS1 (moderate), PM2, and PM3 criteria fulfilled. The strong genotype–phenotype concordance supports potential pathogenicity.

Conclusion:

This is the first report of the c.938del variant and one of the few TALDO1 cases presenting with such a constellation of findings. The case contributes to the expanding clinical and mutational spectrum of transaldolase deficiency. In addition to known hepatic and hematologic features, it emphasizes underrecognized manifestations such as renal stones, skeletal anomalies, and reversible cutis laxa. This report reinforces the diagnostic utility of exome sequencing in unexplained multisystem pediatric conditions.

Keywords:

TALDO1, transaldolase deficiency, exome sequencing, cutis laxa, biliary cirrhosis, multisystemic disorder

FULL TEXTS

FT1- Evaluation of Lymphocyte Cell-Specific Protein-Tyrosine Kinase, G-Protein Signal Regulator 10 and DNA Methyltransferase 1 Gene Expressions in Patients with Ocular Active and Ocular Inactive Behçet's Disease

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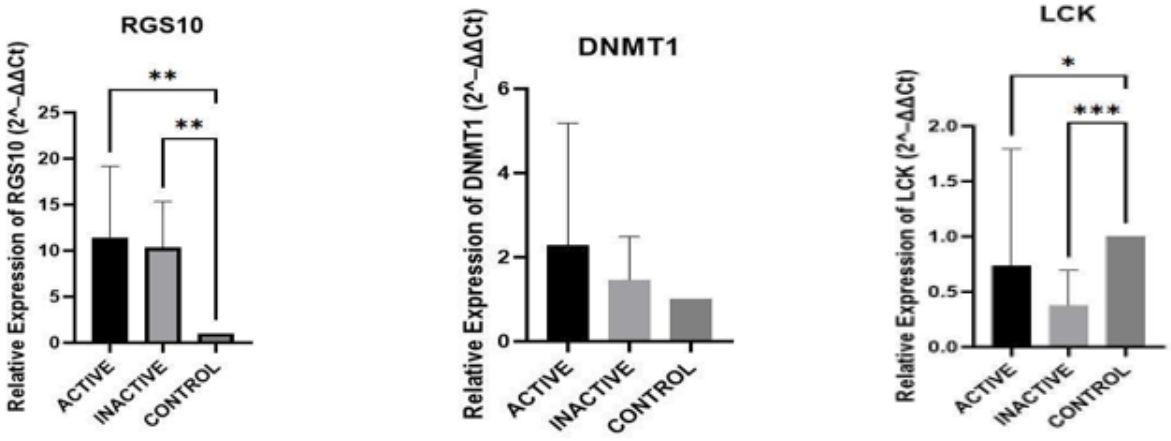
Introduction:
Behçet's disease is a multisystemic disorder with autoimmune and autoinflammatory features, observed more frequently in countries such as China, Japan, and Türkiye (Deng et al., 2022). Clinically, the disease manifests through recurrent oral and genital ulcers, cutaneous lesions, and ocular involvement, which is commonly seen in patients and may lead to vision loss (Guan et al., 2024). Due to the absence of a definitive diagnostic test, diagnosis relies on clinical findings, and genetic predisposition is particularly highlighted in carriers of the HLA-B51 allele (Lavalle et al., 2024). Additionally, environmental factors, infectious agents, and especially epigenetic mechanisms are believed to play a crucial role in disease pathogenesis (Zou et al., 2021; Emmi et al., 2024). One of the key mechanisms of epigenetic regulation is DNA methylation, primarily mediated by DNA methyltransferase-1 (DNMT1) (Zou et al., 2021). DNMT1 is known to influence disease progression by silencing pro-inflammatory genes or modulating anti-inflammatory responses (Caldiran & Cacan, 2022). Moreover, the genes Regulator of G Protein Signaling 10 (RGS10) and Lymphocyte Cell-Specific Protein-Tyrosine Kinase (LCK), which are regulated by epigenetic modifications, have significant roles in the control of immune responses and the pathogenesis of Behçet's disease (Caldiran & Cacan, 2022; Deng et al., 2022). This study aims to investigate the expression levels of DNMT1, RGS10, and LCK genes in patients with ocular involvement in Behçet's disease, thereby contributing to the understanding of immunological and epigenetic mechanisms in disease pathogenesis. Accordingly, it is aimed to provide a scientific basis for identifying disease-specific biomarkers and developing innovative therapeutic strategies.

Materials and Methods:
This study included a total of 45 individuals who were admitted to the Ophthalmology Department of Erciyes University and diagnosed with Behçet's disease (BD) according to international criteria. The participants were divided into three groups:

- BD patients with ocular involvement during the active phase (n = 15)
- BD patients with ocular involvement during the inactive phase (n = 15)
- Healthy control individuals (n = 15)

The control group consisted of systemically healthy individuals without any known ocular or chronic diseases. Informed consent was obtained from all participants. Total RNA was isolated from blood samples collected in EDTA tubes and cDNA synthesis was performed using the iScript cDNA Synthesis Kit. Real-time PCR was conducted using BIO-RAD SSoAdvanced Universal SYBR Green Supermix on a LightCycler 480 (Roche) device to measure mRNA expression levels of the LCK, RGS10, and DNMT1 genes. GAPDH was used as the housekeeping control gene. The project was supported by the Erciyes University Scientific Research Projects Unit with the project code TYL-2025-14428.

Results:
Expression analysis of the RGS10, DNMT1, and LCK genes was performed using real-time PCR, with GAPDH as the reference gene. All group data were statistically analyzed using GraphPad Prism 9.0.0 software.
For the **RGS10 gene**, the Kruskal-Wallis nonparametric test was used due to the non-normal distribution of data across three groups. A statistically significant difference was found between each patient group and the control group ($p < 0.05$), while no significant difference was observed between the two patient groups. The expression of RGS10 was elevated in patient groups compared to the control group.
For the **DNMT1 gene**, data from all groups were normally distributed, and thus, the One-Way ANOVA parametric test was applied. No statistically significant difference was detected between the groups ($p > 0.05$). There was no notable change in DNMT1 expression levels between patient and control groups.
For the **LCK gene**, the Kruskal-Wallis nonparametric test was again used due to non-normal distribution across three groups. A significant difference was observed between each patient group and the control group ($p < 0.05$), but no significant difference was found between the patient groups. Notably, the expression difference in the inactive patient group was more pronounced compared to the active group. The expression level of LCK was decreased in patient groups relative to the control group.



Discussion:

In this study, the effect of ocular involvement associated with Behçet's disease (BD) on immune modulation and epigenetic regulatory mechanisms was investigated by examining the expression levels of the RGS10, DNMT1, and LCK genes. The obtained data suggest that these genes may exhibit significant expression changes in BD patients with ocular involvement.

The increased expression of the *RGS10* gene, especially in BD patients with ocular involvement during the active phase, suggests that this protein may function as a feedback regulator in controlling inflammation. *RGS10* can inhibit G protein signaling, thereby suppressing proinflammatory NF-κB activation and limiting the production of inflammatory cytokines (Ren et al., 2021; Lee et al., 2008). According to our findings, the expression of the *RGS10* gene was significantly elevated in patient groups compared to the control group, which is consistent with the literature. No significant difference in *RGS10* expression was observed between the active and inactive patient groups, suggesting that the expression level of this gene may not vary with the disease phase.

Recent studies have associated altered DNA methylation levels with various autoimmune diseases (Zou et al., 2021). Epigenetic regulatory enzymes such as *DNMT1* are believed to influence disease progression by suppressing the expression of proinflammatory genes or modulating anti-inflammatory responses (Alipour et al., 2017). However, in our study, no significant differences in *DNMT1* gene expression were observed among the groups.

Literature findings support the central role of T cell activation in BD patients with ocular involvement, with *LCK* contributing to increased intraocular inflammation by promoting T cell activation (Deng, 2022). In our study, a significant decrease in *LCK* gene expression was detected in the patient groups compared to the control group, supporting its potential role in BD pathogenesis. Moreover, expression levels were found to be lower in the inactive group than in the active group. This may suggest that *LCK* expression is not only associated with acute inflammation but may also play a role in chronic immune regulation. Accordingly, differential regulation of *LCK* at the peripheral and tissue levels could position it as a potential determinant of both systemic and tissue-specific immune responses.

In conclusion, these findings provide insight into the immunological and epigenetic roles of *RGS10*, *DNMT1*, and *LCK* in BD and may contribute to the identification of disease-specific biomarkers.

References:

1. Alipour, S., Nouri, M., Sakhinia, E., Samadi, N., Roshanravan, N., Ghavami, A., & Khabbazi, A. (2017). Epigenetic alterations in chronic disease focusing on Behçet's disease: Review. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 91, 526–533. https://doi.org/10.1016/j.biopha.2017.04.106
2. Guan, Y., Li, F ., Li ,N ., & Yang, P. (2024). Decoding Behcet's Uveitis; an In-depth rewiev of pathogenesis and therapeutic advances. Journal of neuroinflammation, 21(1), 133 https://doi.org/10.1186/s12974-024-03123-6
3. Lavalle, S., Caruso, S., Foti, R., Gagliano, C., Cocuzza, S., La Via, L., Parisi, F. M., Calvo-Henriquez, C., & Maniaci, A. (2024). Behçet's Disease, Pathogenesis, Clinical Features, and Treatment Approaches: A Comprehensive Review. Medicina (Kaunas, Lithuania), 60(4), 562. https://doi.org/10.3390/medicina60040562
4. Caldiran, F. Y., & Cacan, E. (2022). RGS10 suppression by DNA methylation is associated with low survival rates in colorectal carcinoma. Pathology, research and pratice, 236, 154007. https://doi.org/10.1016/j.prp.2022.154007
5. Zou, Y., Li, J. J., Xue, W., Kong, X., Duan, H., Li, Y., & Wei, L. (2021). Epigenetic Modifications and Therapy in Uveitis. Frontiers in cell and developmental biology, 9, 758240. https://doi.org/10.3389/fcell.2021.758240
6. Emmi, G., Bettiol, A., Hatemi, G., & Prisco, D. (2024).

Behçet's syndrome. Lancet (London, England), 403(10431), 1093–1108. https://doi.org/10.1016/S0140-6736(23)02629-6
7. Lee, J. K., McCoy, M. K., Harms, A. S., Ruhn, K. A., Gold, S. J., & Tansey, M. G. (2008). Regulator of G-protein signaling 10 promotes dopaminergic neuron survival via regulation of the microglial inflammatory response. Journal of Neuroscience, 28(34), 8517-8528.
8. Ren, J., Wei, W., Tan, L., Yang, Q., Lu, Q., Ding, H., ... & Li, J. (2021). Inhibition of regulator of G protein signaling 10, aggravates rheumatoid arthritis progression by promoting NF-κB signaling pathway. Molecular Immunology, 134, 236-246.
9. Deng, Y., Zhang, Y., Cai, T., Wang, Q., Zhang, W., Chen, Z., ... & Yang, P. (2022). Transcriptomic profiling of iris tissue highlights LCK signaling and T cell-mediated immunity in Behcet's uveitis. Journal of Autoimmunity, 133, 102920.
10. Yıldırım, A. (2020). Prevalence and clinical features of Behçet's disease: A retrospective analysis of a cohort of 1,000 patients. Journal of Clinical Rheumatology, 26(2), 91-97. https://doi.org/10.1097/RHU.0000000000001222

FT2- Retrospective Analysis of Mutations Identified in the Beta-Globin Gene in Cases Studied for Beta-Thalassemia Genetics in the Department of Medical Genetics

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Introduction

Beta-thalassemia is a hereditary blood disease characterized by a decrease in erythrocyte and hemoglobin levels, which occurs as a result of mutations or deletions in the Beta-Globin (HBB) gene and is the most common disease worldwide and in our country (1,2). In epidemiologic studies conducted in Turkey, the average incidence of beta-thalassemia was found to be 2.1% and more than 200 mutations were reported (3,4). The most common beta-thalassemia mutations in Turkey include IVS-1-110, IVS-I-6, IVS-I-1, Codon 8, -30 and Codon 5 mutations. The spectrum of beta-thalassemia mutations varies according to regions (4,5). In the literature review, it was noticed that there were deficiencies in the conversion of routine study results into publications. In this study, we investigated the mutation data in the HBB gene in individuals whose beta-thalassemia genetics were studied in our center.

Method

The archival records of 782 individuals who underwent Sanger sequencing analysis for the Beta-Globin (HBB) gene in our center between 2010 and 2024 were retrospectively analyzed.

Results

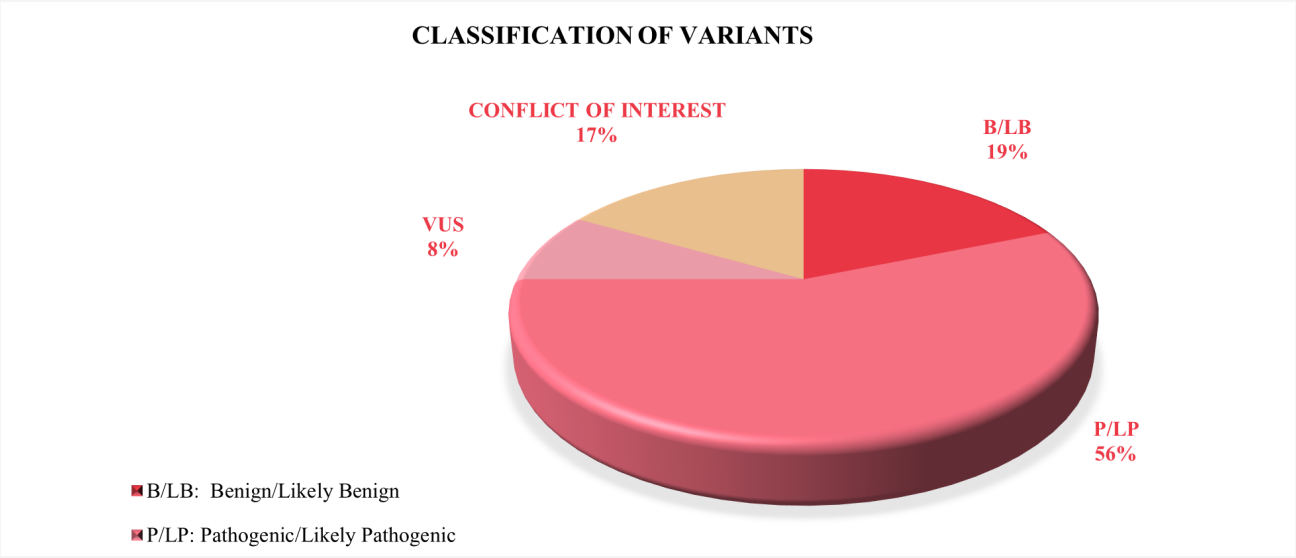
Within the scope of our study, a total of 782 individuals who underwent molecular genetic analysis were statistically evaluated with the SPSS 27.0.1.0 program and 53 different genetic mutations were detected in our center. When the gender distribution of the cases was analyzed, it was determined that 54% were female and 46% were male. According to the data obtained, it was determined that 56% of the mutations were pathogenic/probable pathogenic (P/LP), 53% of the mutations were homozygous and 47% were heterozygous genotypes. Demographic analysis revealed that the highest proportion (22.2%) of the age distribution of the applicants was in the 0-5 age group. When the distribution of previously reported variants in Turkey was analyzed in our center, it was found that the IVSI-110 G>A mutation was the most frequently observed variant with a rate of 22%.

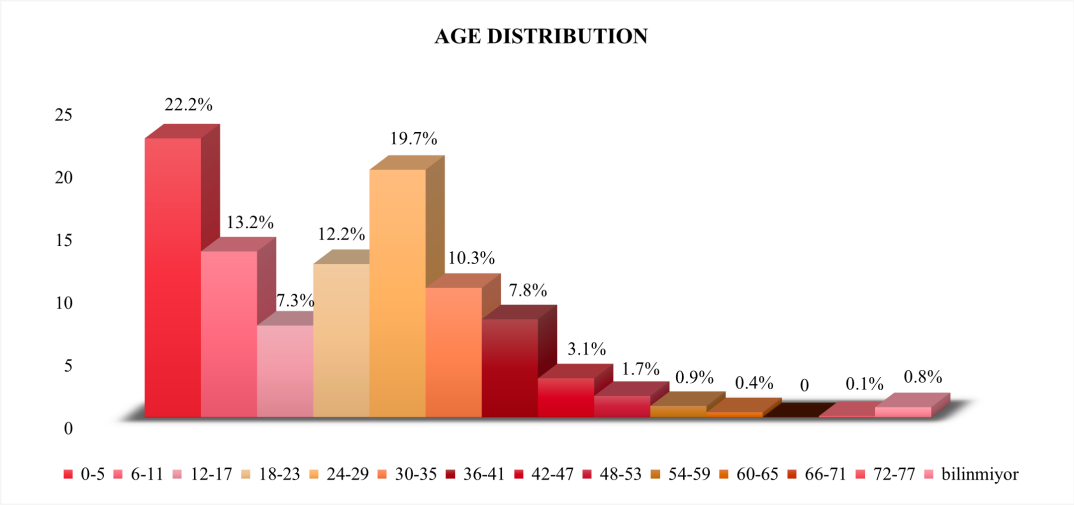
Conclusion

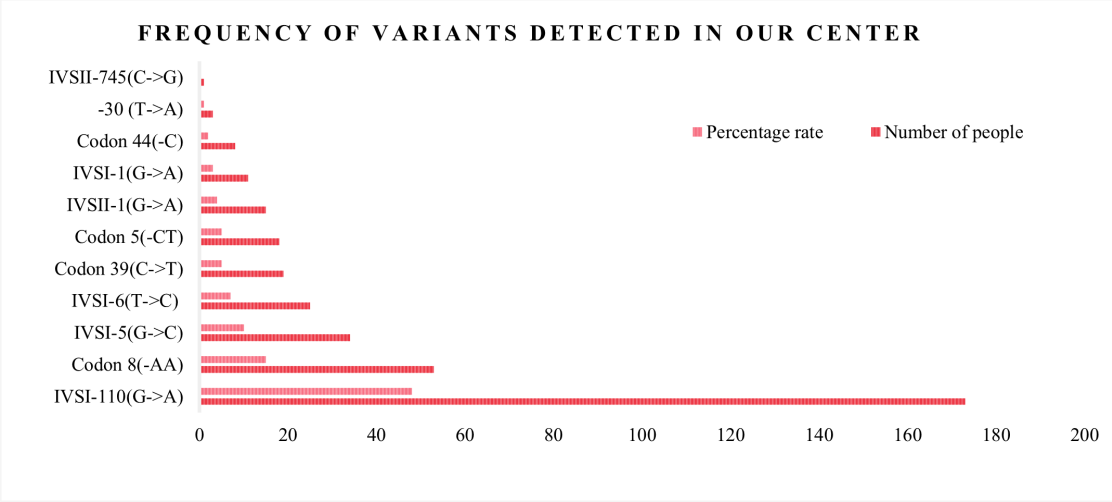
The data obtained in our study provide findings in terms of the clinical classification of genetic mutations, their distribution in the population and the demographic characteristics of the individuals admitted. When the distribution of rare abnormal hemoglobin variants in 37 individuals in our center is examined, the most common variant is Hb D-Los Angeles variant with a rate of 2.1%. Hb City of Hope (0.6%), Hb S (0.6%), Hb G-Coushatta (0.5%), Hb E-Saskatoon (0.3%), Hb Summer Hill (0.1%), Hb D-Iran (0.1%), Hb Volga (0.1%), Hb E (0.1%) variants followed by Hb D-Iran (0.1%). Our study contributes to the identification of new variants associated with Mediterranean anemia and updating genetic data.

Discussion

More than 200 mutations have been reported in the Turkish population. Mutation distributions vary by region due to geographical, ethnic and migration factors (1). In this study, a total of 53 different genetic mutations were identified, including 41 beta-thalassemia mutations and 12 hemoglobin variants. Mutations frequently observed in the Turkish population were also detected in our study (4-5). In line with the literature in Turkey, the most common mutation in our study was IVSI-110 (G>A) with 22%. This rate was reported as 20.65% in the study by Karaer et al. Although the findings were similar, the rate of this mutation was higher in our study (6). Unlike the study by Tadmouri, Codon 8 (-AA) was found to be the second most common mutation with a rate of 15% in our study. IVS I-5 (G>C) was the third most common mutation with a rate of 10%. IVS I-6 (T>C) mutation was identified in 7% of our study. This value is largely compatible with the rate of 7.2% reported by Tadmouri for our region and the rate of 10.33% reported by Karaer et al. This concordance suggests that the variant in question shows a stable distribution in terms of its prevalence in Turkey in general and especially in our region (6-8). The fact that the mutations detected in our center are mostly pathogenic indicates that clinically significant variants are common. Genotype distribution provides important information about the heterozygous (carrier) and disease status of individuals. In the study conducted in our center, a total of 37 individuals with rare hemoglobin variants were examined. It was determined







that 4.4% of these individuals had heterozygous (carrier) form of the variants, while 0.1% were homozygous. The most common Hb D-Los Angeles variant was observed in our center at a rate of 2.1%, which is higher than the rate reported by Güvenç et al. While the Hb E variant (0.1%) was found to be consistent with the literature, the Hb S variant (0.6%) was detected at a lower rate compared to the values reported in the literature (9). The fact that the proportion of individuals aged 0-5 who applied to our center was higher (22.2%) compared to other age groups suggests that awareness of early diagnosis is increasing in society. The findings of this study help address the lack of genetic data on the epidemiology of beta-thalassemia in our

center, clarify the mutation spectrum and support the identification of new variants. Updating genetic diagnostic algorithms will serve as a beneficial guide for the management and prevention strategies of thalassemia, as well as for the more effective planning of future national health policies.

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Keywords: Beta- Thalassemia, Beta-Globin, Mutation, Retrospective, Genetics

References

1. Cho SI, Lee JS, Park SS, Seong MW. Molecular basis and diagnosis of thalassemia. Blood Res, 2021: 56 (S1); S39-S43.
2. Ghani G, Israr M, Lila S, Rahat MA, Rasool A, Saif S. Clinical Insights: Prevalence of β-Thalassemia Mutations (IVSI-5, FSC8/9, and CD41/42) in the Swat District. J Bio-X Res, 2024; 7: 0004.
3. Güntaş G, Öztürk-Kaymak A, Sönmez Ç. Laboratory in thalassemias, a public health problem. Turk Hij ve Den Biyol Derg, 2014: 71(4); 221-8.
4. Canatan D. Thalassemia and Hemoglobinopathies in Turkey (Part 1). Thalassemia and Hemoglobinopathies: Diagnosis-Treatment-Prevention. Nobel Academic Publishing, Ankara 2024; pp: 1-16.
5. Canatan D. Thalassemias and hemoglobinopathies in Turkey. Hemoglobin, 2014: 38(5); 305-7.
6. Karaer D, Sahinoglu B, Sahinoglu EP, Gurler AI, Kırat E, Karaer K. Molecular Spectrum of Beta Thalassemia Mutations in Southeast Turkey. Gazi Med J. 2023: 34(1): 63-67.
7. Tadmouri GO, and Basak AN. β-TALASEMIA IN TURKEY: A CLINICAL, EPIDEMIOLOGICAL, MOLECULAR AND EVOLUTIONARY REVIEW. Hemoglobin, *2001*: 25 (2): 227-239.
8. Tadmouri GO, Tüzmen Ş, Özçelik H, Özer A, Baig SM, Senga EB, Başak AN. Molecular and population genetic analyses of β-Thalassemia in Turkey. Am J Hematol. 1998: 57; 215-220**.**
9. Guvenc B, Canataroglu A, Unsal C, Yildiz SM, Turhan FT, Bozdogan ST, Dincer S, Erkman H. β-Thalassemia mutations and hemoglobinopathies in Adana, Turkey: results from a single center study. Arch Med Sci. 2012: 8(3); 411-4.

FT3- Identification of Key Genes Associated with Alzheimer's Disease through SVM-Based Classification of Cumulative Transcriptomic Data

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease affecting more than 40 million people worldwide and one of the most common causes of dementia (1). In recent years, molecular substructure studies on Alzheimer's disease have increased significantly. Especially high-throughput transcriptomic techniques such as microarray and RNA-seq have allowed the identification of differentially expressed genes (DEGs) in diseased and healthy brain tissues. These genes are often linked to basic cellular processes such as neuroinflammation, synaptic communication, oxidative stress and mitochondrial dysfunction (2). However, most of these studies are limited to statistical approaches and cannot fully reflect the text of the ever-increasing pool of gene expression data. Machine learning (ML) is frequently used to identify complex patterns in high-dimensional datasets within complex biological datasets (3). Support Vector machines (SVM) have been used with very successful results for classification problems obtained with gene expression data (4). However, there are very few studies to date that have combined multiple dated microarray datasets against Alzheimer's disease cumulatively and analyzed them using ML algorithms. This creates opportunities for the discovery of potential biomarkers by combining old and new information. In this study, the microarray dataset of Alzheimer's disease, which was first published in 2004 and reanalyzed in 2010, was re-evaluated in detail with current machine learning techniques.

Methods

Gene expression datasets related to Alzheimer's disease were sourced from two studies (5,6). These datasets were used to create a SVM model for classifying Alzheimer's patients and healthy individuals. The model's performance was enhanced through Monte Carlo cross-validation.

Feature selection identified the most significant genes based on Information Gain Ratio and ANOVA tests, resulting in a final set of 50 genes. To assess these genes as potential biomarkers, we conducted a thorough literature review to examine their associations with Alzheimer's disease, drawing on published studies and evaluating their quality. The validation of the model and the biomarkers depends on their identification in at least 50 relevant studies.

Results

The trained model performs well in differentiating Alzheimer's patients from healthy controls, as evidenced by its classification accuracy (0.968), F1 score (0.968), sensitivity (0.968), specificity (0.971), Matthews correlation coefficient (0.927), and area under the curve (0.995) values. Based on gene expression data, these findings show that the developed SVM model performs a robust and dependable classification.

As a result of a literature review conducted on the 50 most sig-

nificant genes identified through analyses, it was determined that 15 of these genes were directly and significantly associated with AD. ATP6V1D (7), PLCB1 (8) and KIAA0368 (9) genes were identified as hub genes with significant effects on synaptic transmission and neuronal health. MRPL15 (10), ACO2 (11) and DNM1L (12) genes were associated with mitochondrial dysfunction and energy metabolism disorders. KPNA2 (13) and WDFY3 (14) genes contribute to neuronal cell protection by participating in nuclear transport and autophagy mechanisms, respectively. RFK (15) and USP19 (16) genes have been implicated in the regulation of neuroinflammation and ferroptosis processes. While the QPCT (17) gene plays a critical role in the formation of toxic pGlu-Aβ forms, the FGF20 (18) gene shows a protective effect against Alzheimer's pathology by supporting cognitive endurance. The CNR1 (19), C3orf14 (20) and NRXN1 (21) genes have been linked to synaptic function and neuronal communication.

Conclusion

This study aims to develop a reliable machine learning model that can differentiate healthy individuals from patients with Alzheimer's disease using cumulative microarray gene expression data. After preprocessing the data, selecting relevant features, and applying SVM-based classification, 15 key genes were identified, consistent with findings from previous experimental studies. These genes have the potential to contribute to early diagnosis and the development of biomarkers.

Keywords: Alzheimer's disease, support vector machine, gene expression, biomarker

References

1. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegener. 2019 Dec 2;14(1):32.
2. D'Alessandro MCB, Kanaan S, Geller M, Praticò D, Daher JPL. Mitochondrial dysfunction in Alzheimer's disease. Ageing Res Rev. 2025 May;107:102713.
3. Orhan ME, Demirci YM, Saçar Demirci MD. NeRNA: A negative data generation framework for machine learning applications of noncoding RNAs. Comput Biol Med. 2023 Jun;159:106861.
4. Oliveira PP de M, Nitrini R, Busatto G, Buchpiguel C, Sato JR, Amaro E. Use of SVM Methods with Surface-Based Cortical and Volumetric Subcortical Measurements to Detect Alzheimer's Disease. Journal of Alzheimer's Disease. 2010 Mar 11;19(4):1263–72.
5. Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW. Incipient Alzheimer's disease: Microarray correlation analyses reveal major transcriptional and tumor suppressor responses. Proceedings of the National Academy of Sciences. 2004 Feb 17;101(7):2173–8.
6. Gómez Ravetti M, Rosso OA, Berretta R, Moscato P. Uncovering Molecular Biomarkers That Correlate Cognitive Decline with the Changes of Hippocampus' Gene Expression Profiles in Alzheimer's Disease. PLoS One. 2010 Apr 13;5(4):e10153.
7. Duan K, Ma Y, Tan J, Miao Y, Zhang Q. Identification of genetic molecular markers and immune infiltration characteristics of Alzheimer's disease through weighted gene co-expression network analysis. Front Neurol. 2022 Aug 22;13.
8. Xie Z, Situ Y, Deng L, Liang M, Ding H, Guo Z, et al. Identification of therapeutic targets for Alzheimer's Disease Treatment using bioinformatics and machine learning. Sci Rep. 2025 Jan 31;15(1):3888.
9. Wang XD, Liu S, Lu H, Guan Y, Wu H, Ji Y. Analysis of Shared Genetic Regulatory Networks for Alzheimer's Disease and Epilepsy. Biomed Res Int. 2021 Jan 14;2021(1).
10. Du W, Yu S, Liu R, Kong Q, Hao X, Liu Y. Precision Prediction of Alzheimer's Disease: Integrating Mitochondrial Energy Metabolism and Immunological Insights. Journal of Molecular Neuroscience. 2025 Jan 14;75(1):5.
11. Zhang K, Yang K, Yu G, Shi B. Development of a Novel Mitochondrial Dysfunction-Related Alzheimer's Disease Diagnostic Model Using Bioinformatics and Machine Learning. Curr Alzheimer Res. 2024 Dec 26;22.
12. Castora FJ, Kerns KA, Pflanzer HK, Hitefield NL, Gershon B, Shugoll J, et al. Expression Changes in Mitochondrial Genes Affecting Mitochondrial Morphology, Transmembrane Potential, Fragmentation, Amyloidosis, and Neuronal Cell Death Found in Brains of Alzheimer's Disease Patients. Journal of Alzheimer's Disease. 2022 Oct 25;90(1):119–37.
13. Indrigo M, Morella I, Orellana D, d'Isa R, Papale A, Parra R, et al. Nuclear ERK1/2 signaling potentiation enhances neuroprotection and cognition via Importinα1/KPNA2. EMBO Mol Med. 2023 Nov 8;15(11).
14. Deneubourg C, Ramm M, Smith LJ, Baron O, Singh K, Byrne SC, et al. The spectrum of neurodevelopmental, neuromuscular and neurodegenerative disorders due to defective autophagy. Autophagy. 2022 Mar 4;18(3):496–517.
15. Zhang M, Chen H, Zhang W, Liu Y, Ding L, Gong J, et al. Biomimetic Remodeling of Microglial Riboflavin Metabolism Ameliorates Cognitive Impairment by Modulating Neuroinflammation. Advanced Science. 2023 Apr 17;10(12).
16. Yu W, Zhuang S, Zhan M, Chen Y, Zhang J, Chen L, et al. Deubiquitinating Enzyme USP19 Regulates Ferroptosis and Mitochondrial Damage in SH-SY5Y Cells by Targeting the NOX4 Protein. Journal of Alzheimer's Disease. 2024 Jul 30;100(3):799–808.
17. Haque A, Alenezi KM, Abdul Rasheed MohdSM. Identification of imidazole-based small molecules to combat cognitive disability caused by Alzheimer's disease: A molecular docking and MD simulations based approach. Comput Biol Chem. 2024 Oct;112:108152.
18. Insel PS, Kumar A, Hansson O, Mattsson-Carlgren N. Genetic Moderation of the Association of β-Amyloid With Cognition and MRI Brain Structure in Alzheimer Disease.

Neurology. 2023 Jul 4;101(1).
19. Cava C, Castiglioni I. Drug repositioning based on mutual information for the treatment of Alzheimer's disease patients. Med Biol Eng Comput. 2025 Feb 17;
20. Fan Z, Siran Z, Siman Y, Yuting W, Jingjing W, Jinlan H, et al. Identification of Potential Therapeutic Targets of Alzheimer's Disease By Weighted Gene Co-Expression Network Analysis. Chinese Medical Sciences Journal. 2020;35(4):330–41.
21. Tandon R, Levey AI, Lah JJ, Seyfried NT, Mitchell CS. Machine Learning Selection of Most Predictive Brain Proteins Suggests Role of Sugar Metabolism in Alzheimer's Disease. Journal of Alzheimer's Disease. 2023 Mar 21;92(2):411–24.

FT4- Unraveling Post-Transcriptional Regulation in Ataxia-Telangiectasia: A Systems Biology Perspective on microRNA-Target Networks

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Introduction

Ataxia-telangiectasia (AT) is a rare genetic condition related with ATM gene mutations, which control the two cellular processes: DNA double-stranded break repair and cell cycle control (1). The wide range of AT clinical presentations including cerebellar degeneration together with immune deficiency along with cancer predisposition requires moving past traditional genetic explanations since patients exhibit variable treatment outcomes (2). This study examines post-transcriptional gene regulation, with a particular emphasis on microRNAs (miRNAs) (3). These short, non-coding RNAs play a critical role in the precise regulation of mRNA translation, which presents opportunities for the modulation of disease pathways in populations affected by ataxia telangiectasia (AT) (4). Given the complexity and phenotypic variability of AT, this study aims to systematically explore the post-transcriptional regulatory landscape mediated by miRNAs. By integrating RNA-seq and non-coding RNA-seq data, we investigate the interactions between differentially expressed miRNAs and their mRNA targets, perform functional enrichment analyses, and identify critical signaling pathways potentially contributing to AT pathogenesis. The goal is to uncover regulatory hubs and candidate biomarkers that may provide mechanistic insights into the variable clinical outcomes observed in AT and guide future therapeutic strategies.

Methods

RNA-seq and non-coding RNA-seq data related to Ataxia telangiectasia were collectively analyzed to identify significant hub genes and potential biomarkers. To achieve this, we downloaded the RNA-seq data with the GEO number GSE175776 (2) and the non-coding RNA-seq data with the GEO number GSE266411(4). The analysis focused on microRNA-mRNA interactions.

In the data analysis process, differential expression analysis was conducted using the DESEQ2(5) and limma (6) packages in R software. The results of these analyses were filtered based on log2 fold change (log2FC) values less than -2 or greater than 2, and a p-value threshold of less than 0.1 was used to determine statistical significance. The identified genes were categorized as up-regulated or down-regulated, along with related miRNAs.

Targets and network interactions of upregulated and downregulated miRNAs were created using TargetScan (7) and MiRTarBase (8). Experimentally validated strong and weak interactions were sourced from MiRTarBase, and the resulting miRNA networks were designed to include at least three interactions. We compared the expression pattern of miRNAs and mRNAs in Ataxia patients with that of control groups using tidyR and dplyR in RStudio software.

The resulting interactions between hub miRNAs and mRNAs were analyzed using KEGG (9), REACTOME (10), WIKIPATHWAYS (11), and Gene ONTOLOGY(12) analyses to determine the pathways in which they are involved. A reference p-value of less than 0.1 was set for this analysis. The KEGG, REACTOME, and WIKIPATHWAYS analyses were conducted using iDEP 2.0 (13) and MIENTURNET (14). The results of the analysis were visualized with ggplot.

Results

Based on the results of the differential expression analysis, 37 miRNAs were found to be downregulated, while 11 miRNAs were upregulated in patients. Additionally, among individuals with ataxia, 775 mRNAs were upregulated, and only 74 mRNAs were downregulated. The study that analyzed this binary data revealed a significant hub network comprising approximately 150 interactions between downregulated miRNAs and upregulated mRNAs. Within this network, a total of 24 miRNAs were identified as targeting the remaining mRNAs (Figure 1).

Integrative pathway enrichment analysis based on microRNA-target gene associations has identified several signaling pathways that are targeted by microRNAs through at least ten different genes. These pathways represent key regulatory centers that may have significant biological relevance to complex disease mechanisms.

Notably, multiple pathways associated with neurodegenerative diseases emerged as some of the most extensively targeted. Specifically, twelve genes (ATXN1, BCL2, BDNF, CACNA1C, CHRM3, GNAQ, GRM5, KRAS, LRP6, PLCG1, PPP3R1, UBE2G1) are regulated by hsa-miR-30a-5p. This indicates a potential role for this microRNA in synaptic signaling, immune response pathways, and neurodegenerative processes (15).

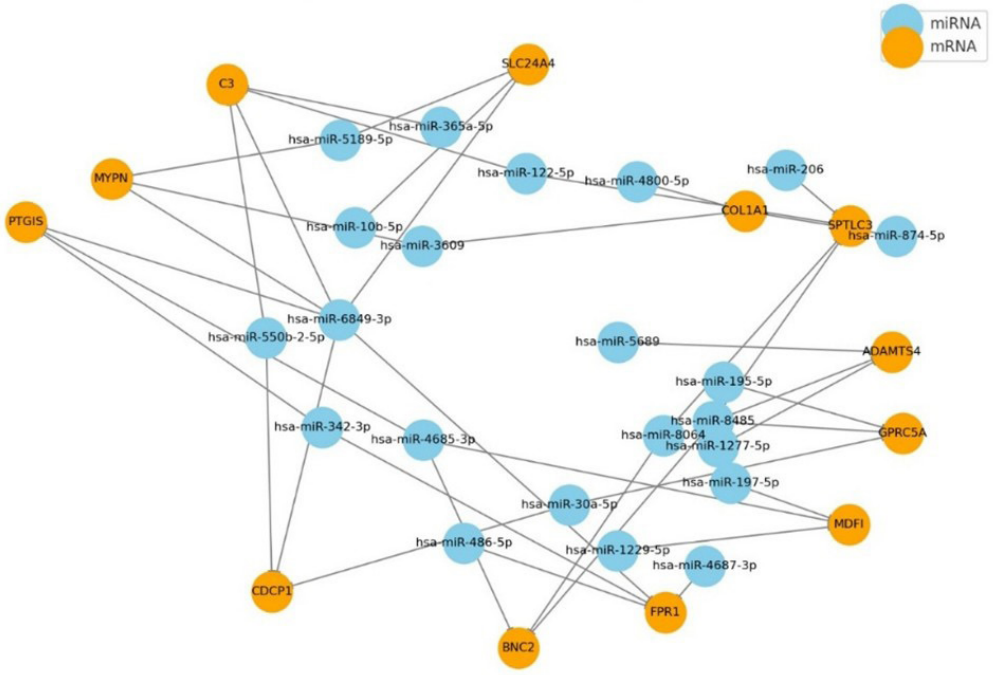

Figure 1. Network analysis determination of miRNAs and mRNAs that have an effect on the development of ataxia telangiectasia disease. According to differential expression analysis, orange nodes represent upregulated genes, while blue nodes represent downregulated miRNAs.

The cellular senescence pathway, which is associated with twelve genes (E2FC, FOXO3, HIPK2, KRAS, NFATC2, NFATC3, PPP3R1, SERPINE1, SMAD2, TSC1, ZFP36L1, ZFP36L2), was also found to be regulated by hsa-miR-30a-5p. This suggests that this microRNA may play a role in cellular metabolism, aging, and proliferation mechanisms (15).

Additionally, the calcium signaling pathway, targeted by seven genes (ATP2B2, CHRM3, EDNRA, FGF9, GNAQ, NFATC2, NFATC3) under the regulation of hsa-miR-195-5p, further emphasizes the importance of miRNA-mediated regulation in calcium-dependent signal transduction and transcriptional control (16).

Conclusion

Expertise in detecting ataxia AT in cerebellar tissue, together with the presence of chromosomal instability and immune dysfunction, suggests that the identified microRNAs may critically impact important disease markers (4,17). Among these miRNAs, hsa-miR-195-5p is particularly noteworthy because it affects DNA damage responses and neuronal survival in AT by targeting pathways related to neurodegeneration and various components of calcium signaling pathways. Additionally, hsa-miR-30a-5p's involvement in metabolic and cardiac signaling may impact the systemic symptoms associated with the condition. Experimental evidence shows that the dysregulation of miRNAs in AT not only relates to variations in outcomes from ATM mutations but also plays a direct role in the variability of clinical presentations. The established networks linking miRNAs, pathways, and genes hold potential as targets for future therapeutic interventions and research validation in the treatment of AT.

Keywords: Ataxia–telangiectasia, miRNA-mRNA interaction, pathway analysis, system biology

References

1. Collyer J, Rajan DS. Ataxia telangiectasia. Semin Pediatr Neurol. 2024 Dec;52:101169.
2. Takahashi T, Stoiljkovic M, Song E, Gao XB, Yasumoto Y, Kudo E, et al. LINE-1 activation in the cerebellum drives ataxia. Neuron. 2022 Oct;110(20):3278-3287.e8.
3. Orhan ME, Demirci YM, Saçar Demirci MD. NeRNA: A negative data generation framework for machine learning applications of noncoding RNAs. Comput Biol Med. 2023 Jun;159:106861.
4. Cirillo E, Tarallo A, Toriello E, Carissimo A, Giardino G, De Rosa A, et al. MicroRNA dysregulation in ataxia telangiectasia. Front Immunol. 2024 Aug 19;15.
5. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014 Dec 5;15(12):550.
6. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015

Apr 20;43(7):e47–e47.
7. Agarwal V, Bell GW, Nam JW, Bartel DP. Predicting effective microRNA target sites in mammalian mRNAs. Elife. 2015 Aug 12;4.
8. Cui S, Yu S, Huang HY, Lin YCD, Huang Y, Zhang B, et al. miRTarBase 2025: updates to the collection of experimentally validated microRNA–target interactions. Nucleic Acids Res. 2025 Jan 6;53(D1):D147–56.
9. Kanehisa M. KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 2000 Jan 1;28(1):27–30.
10. Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, et al. Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics. 2017 Dec 2;18(1):142.
11. Agrawal A, Balcı H, Hanspers K, Coort SL, Martens M, Slenter DN, et al. WikiPathways 2024: next generation pathway database. Nucleic Acids Res. 2024 Jan 5;52(D1):D679–89.
12. Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene Ontology: tool for the unification of biology. Nat Genet. 2000 May;25(1):25–9.
13. Ge SX, Son EW, Yao R. iDEP: an integrated web application for differential expression and pathway analysis of RNA-Seq data. BMC Bioinformatics. 2018 Dec 19;19(1):534.
14. Licursi V, Conte F, Fiscon G, Paci P. MIENTURNET: an interactive web tool for microRNA-target enrichment and network-based analysis. BMC Bioinformatics. 2019 Dec 4;20(1):545.
15. Jiang X, Yuan Y, Tang L, Wang J, Zhang D, Cho WC, et al. Identification and Validation Prognostic Impact of MiRNA-30a-5p in Lung Adenocarcinoma. Front Oncol. 2022 Jan 20;12.
16. Harada M, Luo X, Murohara T, Yang B, Dobrev D, Nattel S. MicroRNA Regulation and Cardiac Calcium Signaling. Circ Res. 2014 Feb 14;114(4):689–705.
17. Borgonio-Cuadra VM, Meza-Dorantes A, Pérez-Hernández N, Rodríguez-Pérez JM, Magaña JJ. In Silico Analysis of miRNA-Regulated Pathways in Spinocerebellar Ataxia Type 7. Curr Issues Mol Biol. 2025 Mar 2;47(3):170.

FT5- Retrotransposon Profiling at CNV Breakpoints in Obese Patients: Insights from a Single-Center Study

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Introduction Copy number variations (CNVs) are genomic structural variations that play a role in the pathogenesis of various genetic traits and diseases.1,2 Transposable elements are DNA sequences that can move within the genome. Initially they were considered as junk DNA, but in recent years they have been recognised as playing active roles in genome evolution and gene regulation.3 Approximately 45% of the human genome is derived from transposable elements. These are DNA transposons and retrotransposons.4 Retrotransposons can be classified into two groups: Long terminal repeats (LTR) and non-LTR. Long interspersed nuclear element (LINE) and short interspersed nuclear element (SINE) families are prominent in non-LTR retrotransposons. Retrotransposons such as LINE, SINE, and LTR are mobile elements that can cause genomic instability by inducing structural rearrangements through RNA-mediated retrotransposition.5-7 Many studies have shown that retrotransposons are associated with breakpoints of CNVs.8 Obesity is a global health problem and a complex disease associated with multiple genetic and environmental factors. Obesity emerges as a result of genetic predispositions interacting with environmental factors. This interaction has increased the interest in epigenetic regulation. This may contribute to the understanding of the disease at the molecular level.9 Findings suggest that the methylation level of retrotransposons, such as LINE-1, may be associated with various phenotypes of obesity and metabolic syndrome.10 The main aim of this study is to identify the retrotransposon profile at the breakpoints of CNVs detected through analyses in a single-centre cohort of obese patients. Based on these data, this study aims to gain insight into the possible mechanisms underlying the structural genomic variations associated with obesity.

Methodology In this study, SNP microarray analysis (Illumina BeadChip Microarray, Infinium HTS, >700K probes) was performed on genomic DNA samples from 47 individuals diagnosed with obesity. The data were analysed using GenomeStudio v2.0.5. During the evaluation of structural variations, only CNVs ranging in size from 50 kilobases (kb) to 5 megabases (Mb) were included in the analysis. These thresholds were set to ensure both the selection of clinically significant variations and technically more reliable results. CNVs suspected to have a mosaic structure or low signal intensity were excluded from the study to minimise possible analysis errors.

Results A total of 126 CNVs that met the criteria determined as a result of CNV analyses were included. The genomic coordinates of the CNVs were determined, and their start and end points (breakpoints) were thoroughly evaluated using the RepeatMasker track in the UCSC Genome Browser to assess the presence, type, and distribution of retrotransposons within these regions. Within the scope of this assessment, regions where repetitive elements of the same class and family were present at both ends of the CNVs were considered potential breakpoints. Analysis of the retrotransposon profiles at the breakpoints of the CNVs included in the obese patient cohort

revealed that 40 CNVs (31.7%) contained the same type of retrotransposon at their breakpoints. It was determined that 35 (87.5%) of these CNVs were associated with the LINE-1 (L1) family, 3 (7.5%) with LINE-2 (L2), and 2 (5%) with the Mammalian-wide Interspersed Repeats (MIR) family. The majority of the CNVs were associated with LINE families, particularly L1.

Discussion

Obesity is a complex disease caused by the interaction of genetic and environmental factors. Epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, are major contributors to interindividual variation, and can influence the risk of obesity.11 Epigenetic changes may even mediate the long-term effects of environmental factors, a phenomenon known as "metabolic memory." 12 Genome-wide association studies have shown single nucleotide polymorphisms associated with obesity. However, these variants are insufficient to fully explain the genetic basis of obesity; therefore, structural variations, particularly CNVs, have gained increasing attention. CNVs are known to cause changes in gene copy number, thereby altering DNA dosage. Some large CNVs may be relatively common in certain populations and appear benign, but when combined with other genomic alterations, they can contribute to disease phenotypes such as obesity.13,14 Our study identified retrotransposons belonging to the same class and family at CNV breakpoints, suggesting that these elements may contribute to genomic instability and the formation of CNVs. Retrotransposons, which constitute the majority of transposable elements, are mobile sequences capable of integrating into various regions of the genome via reverse transcription. The high sequence homology between elements belonging to the same class and family increases the potential for recombination in these regions, thereby predisposing the genome to instability. In particular, the facilitation of non-allelic homologous recombination between non-allelic regions makes this mechanism a major factor in CNV formation.15,16 The prominent presence of LINE elements, particularly those belonging to the L1 family, in our study suggests that these retrotransposons are located in genomic regions that are more prone to structural rearrangements and may have the potential to contribute to CNV formation. The human genome is known to be prone to LINE–LINE recombination events, which contribute to genomic instability and can lead to unbalanced structural variants.17 L1 elements, the most abundant transposons in the human genome, are widely distributed due to their high retrotransposition activity and play a key role in CNV formation.5

L1 elements are known to have significant effects on the structure and genetic diversity of the human genome. Through genetic and epigenetic mechanisms, they can contribute to mutations, structural variations, and a wide range of human diseases.4 One study showed that lower L1 methylation levels in the visceral adipose tissue of severely obese individuals were associated with higher fasting glucose and diastolic blood pressure levels, as well as an increased risk of metabolic syndrome.10 Although not directly identified in our study, Alu elements, an important retrotransposon family, are also associated with structural and epigenetic genomic changes.18 In one study, Alu elements in the intron 2 region of the POMC gene were associated with a hypermethylation variant observed in obese children that increases the risk of obesity by decreasing POMC expression.19 These studies indicate how retrotransposons may contribute to disease risk by influencing the epigenetic regulation of nearby genes.

In conclusion, our study demonstrates that retrotransposons, particularly L1, play a prominent role at CNV breakpoints in individuals with obesity. This finding is in line with the growing evidence that retrotransposons not only predispose the genome to structural alterations, but may also contribute to the development of obesity and related metabolic complications through their methylation status and epigenetic effects on nearby genes. Future studies should investigate retrotransposon-associated structural variations and their epigenetic status in larger cohorts from different populations, as well as in various tissues, particularly in metabolically active tissues and in cell types relevant to obesity. Functional studies are needed to validate the underlying mechanisms, and integrated analyses of genetic and epigenetic data should be conducted.

References

1. Henrichsen CN, Chaignat E, Reymond A. Copy number variants, diseases and geneexpression. *Hum Mol Genet*. Apr 15 2009;18(R1):R1-8. doi:10.1093/hmg/ddp011
2. Pös O, Radvanszky J, Buglyó G, et al. DNA copy number variation: Main characteristics,evolutionary significance, and pathological aspects. *Biomedical Journal*. 2021;44(5):548.
3. Kazazian Jr HH. Mobile elements: drivers of genome evolution. *science*.2004;303(5664):1626-1632.
4. Beck CR, Garcia-Perez JL, Badge RM, Moran JV. LINE-1 elements in structural variation anddisease. *Annual review of genomics and human genetics*. 2011;12(1):187-215.
5. Cordaux R, Batzer MA. The impact of retrotransposons on human genome evolution. *Nat RevGenet*. Oct 2009;10(10):691-703. doi:10.1038/nrg2640
6. Bourque G, Burns KH, Gehring M, et al. Ten things you should know about transposableelements. *Genome Biology*. 2018/11/19 2018;19(1):199. doi:10.1186/s13059-018-1577-z
7. Hancks DC, Kazazian HH. Roles for retrotransposon insertions in human disease. *MobileDNA*. 2016;7:1-28.
8. Korbel JO, Urban AE, Affourtit JP, et al. Paired-end mapping reveals extensive structuralvariation in the human genome. *Science*. 2007;318(5849):420-426.
9. Say Y-H. The association of insertions/deletions (INDELs) and variable number tandemrepeats (VNTRs) with obesity and its related traits and complications. *Journal of PhysiologicalAnthropology*. 2017/06/14 2017;36(1):25.

doi:10.1186/s40101-017-0142-x
10. Turcot V, Tchernof A, Deshaies Y, et al. LINE-1 methylation in visceral adipose tissue ofseverely obese individuals is associated with metabolic syndrome status and related phenotypes. *ClinEpigenetics*. Jul 2 2012;4(1):10. doi:10.1186/1868-7083-4-10
11. Ouni M, Schürmann A. Epigenetic contribution to obesity. *Mamm Genome*. Jun 2020;31(5-6):134-145. doi:10.1007/s00335-020-09835-3
12. Rosen ED, Kaestner KH, Natarajan R, et al. Epigenetics and Epigenomics: Implications forDiabetes and Obesity. *Diabetes*. Oct 2018;67(10):1923-1931. doi:10.2337/db18-0537
13. Bochukova EG, Huang N, Keogh J, et al. Large, rare chromosomal deletions associated withsevere early-onset obesity. *Nature*. 2010;463(7281):666-670.
14. Li W, Olivier M. Current analysis platforms and methods for detecting copy number variation.*Physiol Genomics*. Jan 7 2013;45(1):1-16. doi:10.1152/physiolgenomics.00082.2012
15. Cardoso AR, Oliveira M, Amorim A, Azevedo L. Major influence of repetitive elements ondisease-associated copy number variants (CNVs). *Hum Genomics*. Sep 23 2016;10(1):30.doi:10.1186/s40246-016-0088-9
16. Robberecht C, Voet T, Zamani Esteki M, Nowakowska BA, Vermeesch JR. Nonallelichomologous recombination between retrotransposable elements is a driver of de novo unbalancedtranslocations. *Genome Res*. Mar 2013;23(3):411-8. doi:10.1101/gr.145631.112
17. Startek M, Szafranski P, Gambin T, et al. Genome-wide analyses of LINE–LINE-mediatednonallelic homologous recombination. *Nucleic Acids Research*. 2015;43(4):2188-2198.doi:10.1093/nar/gku1394
18. Kuehnen P, Krude H. Alu elements and human common diseases like obesity. *Mob GenetElements*. Jul 1 2012;2(4):197-201. doi:10.4161/mge.21470
19. Kuehnen P, Mischke M, Wiegand S, et al. An Alu element-associated hypermethylation variantof the POMC gene is associated with childhood obesity. *PLoS Genet*. 2012;8(3):e1002543.doi:10.1371/journal.pgen.1002543

FT6- The Importance Of Polymorphism And Alleles Of The NPY Gene In Metabolic Syndrome And It Is Components

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Introduction

Metabolic syndrome (MetS) is a systemic metabolic disorder and represents one of the most pressing issues in modern medicine. The main components of MetS include: abdominal obesity, insulin resistance, arterial hypertension, and dyslipidemia (1). The neuropeptide Y (NPY) gene plays an important role in the regulation of energy balance, appetite and metabolism (2). The NPY gene encodes a 36-amino acid neuropeptide that is involved in various physiological and homeostatic processes both in the central and peripheral nervous systems (3,4). Some of its polymorphisms are associated with an increased risk of developing MetS including obesity, insulin resistance, and lipid metabolism disorders. An association has been confirmed between the NPY gene allele and impaired glucose tolerance as well as the development of insulin resistance (5,6).

Methods

A cross-sectional descriptive study was conducted involving 190 patients. All participants underwent assessment of anthropometric parameters (waist circumference ≥94 cm in men and ≥80 cm in women), blood pressure measurement (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg) and evaluation of blood triglycerides, glucose and lipid levels (triglycerides ≥1.7 mmol/L, HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women and fasting glucose ≥5.6 mmol/L). MetS was diagnosed according to the IDF (2005) criteria. All patients underwent genotyping to identify a single nucleotide polymorphism (SNP) of the NPY gene using the PCR-RFLP method. Patients with incomplete examination or genotyping data were excluded from the statistical analysis (6 patients). The remaining participants were divided into two groups: those with MetS (n=120) and those without MetS (n=70). Statistical analysis was performed using the SPSS 25 program. The study was approved by the Ethical Committee of the International Kazakh-Turkish University named after H.A. Yasavi (protocol No. 30 dated 30.05.2024).

Results

The prevalence of genotypes and alleles of the NPY gene polymorphism was studied. The mean age of the participants was 49.78±11.1 years. According to the results of the genetic analysis the distribution of NPY gene genotypes and alleles was as follows: CC genotype – 17.9%, TC genotype – 56.8%, TT genotype – 22.1%. The frequency of the C allele was 48.6%, and the T allele – 51.4%. A statistically significant positive association was found between the T allele and the component of MetS represented by fasting hyperglycemia (χ^2=4.04, p=0.032). No statistically significant associations were found for the other components of MetS.

Conclusion

Thus, the association of the NPY gene polymorphism may play a significant role in predisposition to the components of metabolic syndrome. In our study, the T allele was more frequently observed in patients with fasting hyperglycemia. The NPY gene carrying the T allele may contribute to a more adaptive stress response by reducing cortisol release, thereby preventing an increase in blood glucose levels — this is particularly important in individuals predisposed to diabetes and MetS. Genetic testing for these polymorphisms could serve as a useful tool for assessing the risk of developing MetS and has clinical relevance for the prevention and treatment of metabolism-related diseases.

Keywords
NPY gene polymorphism, metabolic syndrome, metabolic components, impaired glucose

References

1. Huang Y, Lin X, Lin S. Neuropeptide Y and Metabolism Syndrome: An Update on Perspectives of Clinical Therapeutic Intervention Strategies. Front Cell Dev Biol. 2021 Jul 9;9:695623. doi: 10.3389/fcell.2021.695623. PMID: 34307371; PMCID: PMC8299562/
2. de Luis DA, Izaola O, de la Fuente B, Primo D, Aller R. Association of Neuropeptide Y Gene rs16147 Polymorphism with Cardiovascular Risk Factors, Adipokines, and Metabolic Syndrome in Patients with Obesity. J Nutrigenet Nutrigenomics. 2016;9(5-6):213-221. doi: 10.1159/000452131. Epub 2016 Oct 28. PMID: 27788523.
3. Zhang Q, Wan Y, Du X, Gao Y, Wang X, Wu K, Zheng X, Wang Y, Zhao C, Li L, Guo X, Li X, Liu S, Xu Y. Association between neuropeptide Y gene polymorphism and antipsychotics effect. Front Psychiatry. 2022 Oct 21;13:1014952. doi: 10.3389/fpsyt.2022.1014952. PMID: 36339882; PMCID: PMC9633956.
4. Daniel Antonio de Luis, Olatz Izaola, Beatriz de la Fuente, David Primo, Rocio Aller; Association of Neuropeptide Y Gene rs16147 Polymorphism with Cardiovascular Risk Factors, Adipokines, and Metabolic Syndrome in Patients with Obesity. Journal of Nutrigenetics and Nutrigenomics 6 April 2017; 9 (5-6): 213–221.
5. Parizadeh, S. A., Jamialahmadi, K., Rooki, H., Zaim-Kohan, H., Mirhafez, S. R., Hosseini, N.,Ghayour-Mobarhan, M. (2014). Association of neuropeptide Y gene rs16147 polymorphism with metabolic syndrome in patients with documented coronary artery disease. Annals of Human Biology, 42(2), 179–184. https://doi.org/10.3109/03014460.2014.916750
6. Penes, O.N.; Weber, B.; Pop, A.L.; Bodnarescu-Cobanoglu, M.; Varlas, V.N.; Kucukberksun, A.S.; Cretoiu, D.; Varlas, R.G.; Zetu, C. Gene Polymorphisms LEP, LEPR, 5HT2A, GHRL, NPY, and FTO-Obesity Biomarkers in Metabolic Risk Assessment: A Retrospective Pilot Study in Overweight and Obese Population in Romania. Cardiogenetics 2024, 14, 93-105. https://doi.org/10.3390/cardiogenetics14020008